Circulation
The Journal of the American Heart Association

FEBRUARY 1952
VOL. V NO. 2

The George E. Brown Memorial Lecture

The Pathogenesis and Treatment of Thrombosis

By IRVING S. WRIGHT, M.D.

The present knowledge regarding the pathogenesis of thrombosis is reviewed. New conceptions and technics involving physical principles are outlined. Hitherto unemphasized aspects of thrombosis are discussed. The present status of anticoagulant therapy is summarized. The effects of other factors on the action of anticoagulants are considered.

THROUGHOUT his entire existence man is almost constantly hemorrhaging and thrombosing. It is true that the loss of blood is for the most part small and that the thromboses are just adequate to close the breaks in the minute vessels, but the neat balance between the extremes of continued massive hemorrhage and universal clotting is worthy of our most careful study. Perhaps the key question, as Dr. Best has put it, is not why thromboses occur, but rather, why blood remains fluid for most of our lives.

Studies of thrombosis were first largely carried on by pathologists interested in the gross appearance of clots and, later, in microscopic examination of their cellular components. More recently, Knisely and his co-workers[1] have focused attention on the hemodynamics which may play a part in setting the stage for thrombosis. The biochemists have developed schematic outlines of the chemical actions which take place in the noncellular components of the plasma, although more recently they have included the platelets in their observations.

Critical studies are now being carried on with isolated fractions of the blood such as fibrinogen, prothrombin, Ac-globulin and thrombin. The physical chemists, going one step further, are studying the molecular structure and the actions of certain of these components and other physical factors, such as the electrical charges which may have influence in terms of repulsion or attraction of molecules to the walls of the vessels and to each other.

Certain facts should be emphasized in order that one does not lose sight of the problem as a whole.

(1) Blood is a mixture of a great many components, some of which have probably not even been recognized as yet. In any thrombus in vivo *most* of these components become involved and many of them play a significant role in the formation of the thrombus.

(2) In disease states the occurrence of thromboembolic phenomena does not proceed in the orderly fashion suggested by schematic outlines. At the same instant many stages of the process may be taking place: chemical, physical, physiologic and pathologic. All schematic presentations must of necessity be oversimplified; the whole process is enormously complex.

(3) The clotting tendency, as measured by clotting time tests or prothrombin time tests determined from blood taken from the antecubital veins, may bear little relationship to the clotting tendency in distant areas of the body, as, for example, areas where local injury to tissue is being produced by trauma or cancer. While these tests are helpful, therefore, there

Delivered before the Twenty-fourth Annual Scientific Session of the American Heart Association, Atlantic City, N. J., June 8, 1951.

should be no great surprise when thrombi occur in the presence of what are thought to be therapeutic levels of anticoagulant therapy.

An endeavor will be made to outline some of the findings and hypotheses based on recent work. To fit them into their proper places in this extremely complex and rapidly changing field of medicine is manifestly impossible at this time. It may even be presumptuous to bring them together into a single lecture.

Historically, and from the viewpoint of the anatomic pathologist, one's natural inclination is to consider the gross and microscopic appearance of a thrombus. However, it is clear that the initial steps of the clotting mechanism are either chemical or physical, and probably these cannot be clearly differentiated. Therefore we will arbitrarily use the chemical changes as our point of departure. Dr. Walter Seegers in his George E. Brown Memorial Lecture of 1949 outlined the chemical aspects of this problem in considerable detail.

Biochemical Aspects

The "classic theory" of blood coagulation has been represented by the two equations shown in figure 1.

I. Prothrombin (1) + Thromboplastin (2) + Calcium (3) → Thrombin

II. Fibrinogen (4) —Thrombin→ Fibrin

Fig. 1. Classic theory of blood coagulation.

This mechanism was originally proposed by Morawitz in 1905 and has been regarded as a simplified version of the manner in which four recognized factors in the blood react to produce a fibrin clot. The general acceptance of this simplified concept is probably responsible for tardiness in seeking new facts and for the confusing and controversial nature of the extensive literature in this field. The recent discovery of additional clotting factors has further complicated matters.

In 1943 Quick[2] challenged the classic theory of blood coagulation. He reported that prothrombin consisted of two components. His experimental findings were confirmed in several other laboratories. Approximately a year later Owren[3] described a new factor, which he called factor V. It is now generally assumed that Quick's original component A, which he now designates as "labile factor" and which was first believed to be an unstable form of prothrombin, is actually a protein which accelerates the conversion of prothrombin to thrombin. This new factor has been found to be a globulin and was named "accelerator globulin (ACG)" by Seegers.[4]

When purified prothrombin is used in the first reaction above, thrombin is liberated very slowly. However, if Ac-globulin is added in small amounts, the rate of conversion of prothrombin to thrombin is tremendously accelerated. The mechanism by which Ac-globulin affects this rate of conversion is not known and there is disagreement among various investigators. Owren first reported some alteration in activity during coagulation and suggested that factor V was changed to the active substance, factor VI, during coagulation. Seegers and his group also noted this change in activity and found that the addition of a small amount of thrombin was all that was necessary for the activation of an inert plasma Ac-globulin to active serum Ac-globulin. Whether this activation of Ac-globulin was due to thrombin or to one of the other reaction products produced during the conversion of prothrombin to thrombin has not been definitely established.

The work of Nolf,[5] Quick,[2] Owren,[3] Fantl,[6] and Seegers[4] would indicate that the classic theory to which we referred above should be changed in order to fit these recent observations (fig. 2).

Alexander[7] and Jacox[8] have reported the presence of serum prothrombin conversion ac-

I. Prothrombin —Calcium ions, Thromboplastin (Slow reaction)→ Thrombin

II. Plasma ACG (inert) —Thrombin (Small amount)→ Serum ACG (active)

The serum ACG then increases the rate of reaction I.

III. Prothrombin —Calcium ions, Thromboplastin, Serum ACG (rapid reaction)→ Thrombin

IV. Fibrinogen —Thrombin→ Fibrin

Fig. 2. Modern theory of blood coagulation.

celerators. Quick[9] has also reported another factor which he considers necessary to explain certain hypoprothrombinemias that could not be attributed to the known clotting factors. Recently Owren[10] reported still another factor that is required for thrombin formation. These substances are in some ways very similar to serum Ac-globulin, but in other respects entirely different.

The true significance of these factors in blood coagulation will be determined when they are isolated in pure form and their identity and mechanism of action determined.

Calcium is also required for the activation of prothrombin, but the mechanism of action of such a relatively simple chemical entity as the calcium ion in this phase of blood coagulation is not known. Recently its necessity has actually been questioned, since prothrombin can be converted to thrombin without its presence in oxalated plasma systems[11] as well as in purified systems.[12] It is now being recognized, however, that calcium may influence the type and structure of the fibrin clot formed during blood coagulation.

The remaining substance, thromboplastin or thrombokinase, completes the list of recognized essential factors involved in the activation and conversion of prothrombin to thrombin. Thromboplastin is considered to be a lipoprotein and very active preparations are obtained from brain, lung and placental tissues. Thromboplastin activity has been shown to be present in practically all tissues of the body and also in urine, saliva and human milk.

Very little is known concerning the exact mode of action of this material.[11] It appears to be potentially available in blood, and one of the important problems at present relates to its activation. This initiating step in coagulation has long been neglected. Some investigators believe that an activator present in platelets is necessary, while others believe that an inhibitor controls its activity.[11, 13, 14]

The final reaction in the coagulation of blood is considered to be the reaction between the proteins fibrinogen and thrombin to form a solid structure of fibrin. The conversion of fibrinogen to fibrin can be considered to be a polymerization of fibrinogen units which are transformed into fibrin by a two step reaction. Thrombin activates fibrinogen; that its action is enzymatic is one fact in the mechanism of blood coagulation that is fairly well established. The slow progress in establishing the exact mechanism of interaction of the blood components necessary for clotting is due in large part to the complexity of the various phases of coagulation.

Exploration into the Field of Physical Chemistry As it May Be Related to Blood Clotting

While great credit must be given to those who have explored and elucidated, in part, the physiologic, pathologic and biochemical aspects of thrombosis, it has long seemed clear that we must search further into the realm of even more basic facts if we are ever to comprehend this phenomenon fully. As outlined above, the clotting mechanism requires the conversion of fibrinogen into fibrin, but at the Fourth Conference on Blood Clotting of the Josiah Macy, Jr. Foundation, Laki and others expressed the opinion that there is an intermediary substance which may be called profibrin. Thrombin is, as previously stated, essential to this reaction; so far, so good; but what actually does take place and why? At this and at all other points in the entire process we must probably turn to physical chemistry for our basic answers. The fibrinogen molecule is a long, very thin rod which normally rotates rapidly on its axes and which remains isolated from other molecules of fibrinogen until the conversion reaction to fibrin takes place. At that time, these long, slender molecules join others end to end and side to side forming a network of laminated strands. They cease to rotate on their long axis, but movement may continue in terms of rotation on their cylindrical axis. This network becomes tough and sticky and forms the nucleus for subsequent clot formation.[15, 16]

As part of a team of workers from the Chemistry Department, School of Electrical Engineering and the Cornell University Medical College,[17, 18] we have been studying the factors which keep the fibrinogen molecules and all other constituents of the blood apart and prevent adhesion to the walls of the blood vessels,

and have been exploring the possible significance of electrical forces in this regard.

Following the fundamental law that two objects with similar charges are mutually repulsive, it has been suggested that such mutual repulsion may play some part in preventing the components of the blood from coming together for clot formation. It has been recognized since 1886 (Freund[18]) that the surface properties of vessels play a major part in the rapidity of blood clotting in vitro. Freund worked with paraffin- and vaseline-lined vessels and, more recently, collodion and silicone coatings have been used. All these substances pro-

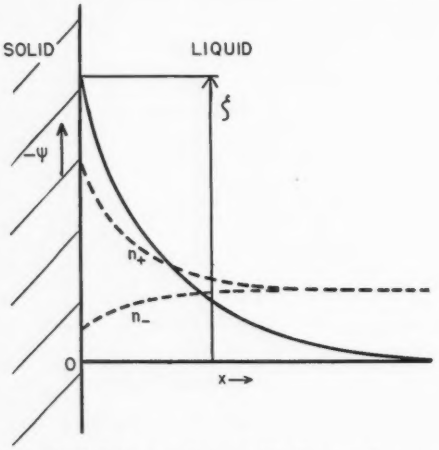


FIG. 3. Relative variation with distance from surface of the electric potential (solid curve) and the concentrations of positive and negative ions (dashed curves). The positive ions are attracted to the wall and the negative repelled.

long the clotting time markedly as compared with glass. They are nonpolar in character and nonwettable by water. In contrast to these and other organic materials, glass is a substance which has strongly polar or electrovalent bonds between its constituent atoms, even the least polar being about 50 per cent electrovalent (Pauling[19]).

This polarity gives rise to strong electrical forces in the neighborhood of the surface of the substance in contact with solutions, and to this polarity may be ascribed a variety of surface phenomena such as preferential adsorption of polar substances or the occurrence of electrical charges at interfaces between liquids and solids. In solid-liquid systems these charges give rise to a potential difference between the interface of the glass and the liquid, on the one hand, and the interior of the liquid on the other. This potential difference is known as the zeta potential, and it is precisely measurable in a large variety of systems.

The influence of the surface of the vessel upon clotting in vivo as well as in vitro has long been recongized as important by pathologists. Vessel walls injured by whatever cause are often the site of thrombosis, whereas blood tied off within a normal vessel will remain unclotted for a long time.

The possibility that the anticoagulant substances may function in part on the basis of their effect on electrical charges was suggested by the findings of Chargaff and his co-workers[20] and Wolfram.[21] Heparin, for example, behaves in solutions as a highly charged anion and migrates in the electrical field toward the anode.

These and other considerations led us to a study of the zeta potentials of glass and silicone-coated surfaces in contact with blood, protein fractions of blood, and various anticoagulants, with the anticipation that interesting data might well be obtained.

Definition of the Zeta Potential

A solid surface in contact with a solution generally is electrically charged, but the mechanism by which the charges arise on the surface is not fully understood. It is presumably a result of selective adsorption of certain ions from the contained solution. As a result of such charges, which are usually negative, the ions in the solutions will not have the same concentration in the neighborhood of the wall as they do in the center of the solution. The positive ions will be attracted toward the wall and the negative will be repelled in the situation shown in figure 3. Far from the wall the potential will approach zero and the ion concentration will be that of the bulk solution. The zeta potential is the difference between the wall potential and that of the interior of the solution, which is arbitrarily taken as zero.

The zeta potential is most accurately measured by producing streaming potentials, which

result when a liquid is forced through a capillary. Figure 4 shows schematically why the streaming potential arises in such an experiment. When the liquid flows through the tube indicated in lengthwise section, the positive ions present in excess in the solution are carried along in the direction of the flow and give the efflux end of the tube a positive charge. As this charge builds up, a flow of electric current back through the tube begins, since the solution is a conductor (only the excess positive ions in the solution are shown in the figure). When the tendency of the liquid flow to sweep the positive ions of the electric double layer along the tube is exactly counterbalanced by the counterflow of ions under the influence of the electric potential difference, a steady potential difference between the ends of the tube results. This is known as the streaming potential. The zeta potential is calculated from the streaming potential value.

The details of the fomulas and apparatus used in these studies have already been published elsewhere and will not be included in this presentation.[17, 18]

An attempt will be made to summarize briefly some of the results of the past four years of work in our laboratories with the zeta potential measurements.

It was found very early that changes in the pH exerted a considerable effect on the zeta potentials. This was to be expected since surfaces in contact with proteins generally become coated with proteins and thereafter exhibit properties characteristic of the protein.

The Effect of Heparin on the Zeta Potential of Blood (fig. 5). While there is no significant difference in the behavior of the blood in the vitreous silica and silicone-coated capillaries, the addition of heparin increases the negative charge very substantially. In this experiment the amount of heparin is large in proportion to the blood sample.

In addition, similar studies were carried out using nonclotting (oxalated) plasma, clotting plasma (prepared by centrifuging the venous blood in a silicone-coated tube) and serum. In each instance the addition of heparin definitely increased the negative potentials. (See fig. 6.)

The Effect of Heparin on the Zeta Potentials of Plasma Fractions. The results of zeta potential studies with several bovine plasma fractions agreed qualitatively with those obtained by electrophoresis of plasma; namely, the al-

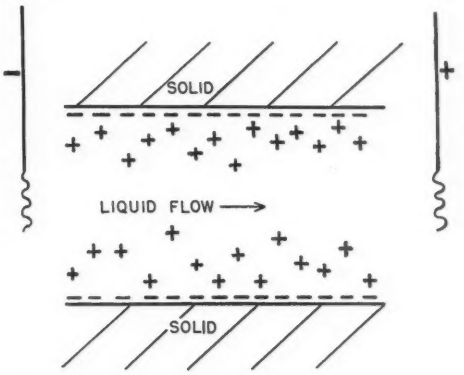


FIG. 4. Schematic diagram of capillary in lengthwise section, showing negative charges on wall, and positive charges in solution.

Additive Amt/100 ml. Phosphate	Vitreous Silica Capillary		Silicone-Coated Capillary	
	pH	Zeta-Potential (Mv.)	pH	Zeta-Potential (Mv.)
0.05 ml. blood	6.9	− 6	6.9	− 8
0.05 ml. blood +5 mg. heparin	6.6	−45	6.6	−41
5 mg. heparin	6.9	−89	6.9	−84
5 mg. heparin +0.05 ml. blood	6.7	−43	6.7	−51
0.05 ml. washed red cells	7.1	−11	—	—

FIG. 5. Effect of heparin on the zeta-potential of blood.

Additive Amt/100 ml. Phosphate	Vitreous Silica Capillary		Silicone Coated Capillary	
	pH	Zeta-Potential (Mv.)	pH	Zeta-Potential (Mv.)
0.05 ml. plasma (oxalated)	6.9	− 10	6.8	− 10
0.05 ml. plasma (oxalated) +5 mg. heparin	6.8	− 23	6.8	− 23
1.0 ml. plasma (oxalated)	6.8	− 12	6.8	− 9
1.0 ml. plasma (oxalated) +5 mg. heparin	6.8	− 22	6.8	− 15
0.05 ml. plasma (clotting)	6.8	− 14	6.7	− 13
0.05 ml. plasma (clotting) +5 mg. heparin	6.8	− 35	6.7	− 33
0.05 ml. serum (no oxalate)	6.6	− 17	6.6	− 17
0.05 ml. serum (no oxalate) +5 mg. heparin	6.4	− 29	6.3	− 24

FIG. 6. Effect of heparin on the zeta-potentials of plasma A.

bumin boundary moves the fastest in the electric field and therefore carries the greatest negative charge, whereas the mobility of fraction II, 100 per cent gamma globulin, is the lowest and consequently has the smallest negative charge.

Additive Amt./100 ml. Phosphate	Vitreous Silica Capillary		Silicone-Coated Capillary	
	pH	Zeta-Potential (Mv.)	pH	Zeta-Potential (Mv.)
5 mg. fibrinogen	6.7	−20	7.1	−24
5 mg. heparin	6.7	−64	6.6	−44
5 mg. heparin +5 mg. fibrinogen	6.6	−37	6.8	−40
5 mg. paritol	6.7	−63	6.7	−54
5 mg. paritol+5 mg. fibrinogen	6.7	−32	6.7	−29
5 mg. "phosphatide inhibitor"	6.7	−69	6.8	−85
5 mg. "phosphatide inhibitor"+5 mg. fibrinogen	6.7	−39	6.7	−53
5 ml. 1,5-pentanodiol*	4.2	−11	4.2	−14
5 ml. 1,5-pentanodiol* −0.03 ml. blood	4.4	+18	4.4	+19

* 100 ml. of 0.001 M KCl solution was used in place of the 100 ml. of phosphate solution

FIG. 7. Effect of other anticoagulants on the zeta-potentials.

Additive Amt./100 ml. Phosphate	ZETA-POTENTIAL (Mv.)			
	pH	Vitreous Silica Capillary	pH	Silicone-Coated Capillary
5 mg. thrombin	6.7	−39	5.8	−20
5 mg. thrombin +5 mg. heparin	6.7	−44	6.4	−45
5 mg. thromboplastin	6.7	−29	6.7	−28
5 mg. thromboplastin +5 mg. heparin	6.6	−56	6.6	−35
5 mg. protamine	7.0	+30	6.6	+32
5 mg. protamine+5 mg. heparin	7.0	−46	7.0	−44
5 mg. heparin	6.7	−64	6.6	−44

FIG. 8. Effect of heparin on the zeta-potentials of other blood clotting substances.

Additive Amt./100 ml. 0.001 N KCl	ZETA-POTENTIAL (Mv.)	
	Vitreous Silica Capillary	Silica-Coated Capillary
5 mg. heparin	−96	−66
5 mg. heparin+5 mg. protamine	−64	−45
5 mg. heparin+10 mg. protamine	− 1	− 1
5 mg. heparin+15 mg. protamine	− 2	− 0.5
5 mg. protamine	+37	+32
15 mg. protamine	+29	+21
15 mg. protamine+5 mg. heparin	+ 5	+ 2

FIG. 9. Antagonism of protamine vs. heparin.

Heparin makes the zeta potentials of fraction II, fraction III-1 (88 per cent gamma globulin, 10 per cent alpha globulin and 2 per cent albumin) and fibrinogen more negative, whereas it has little or no effect on the crystalline albumin and fraction IV (55 per cent albumin, 20 per cent beta globulin and 25 per cent alpha globulin).

Effect of Other Anticoagulants on the Zeta Potentials (fig. 7). After noting the changes produced by heparin it was of interest to see whether other anticoagulants produced the same effects. Accordingly, studies of a similar nature were conducted with Paritol (a polysulfuric acid ester of polyanhydromannuronic acid) and with the phosphatide inhibitor isolated in our laboratory by Overman. It was found that both of these anticoagulants behave similarly with fibrinogen in that they cause the zeta potential to become more negative. However, 1,5-pentanediol, which Ferry found to inhibit the action of thrombin on fibrinogen, has no effect on the zeta potential of blood, which is not surprising in view of its nonionic nature.

Effect of Heparin on the Zeta Potentials of Other Blood Substances (fig. 8). Inasmuch as the production of thrombin by the action of thromboplastin on prothrombin is one of the first steps in blood clotting, the effect of heparin on the zeta potentials of these substances was of interest. The zeta potentials of thrombin and thromboplastin were rendered more negative by the addition of heparin, thrombin being more markedly affected.

It was of especial interest that protamine, which counteracts the effect of heparin physiologically, can, in sufficient quantities, apparently counteract the negative zeta potential action of heparin (fig. 9). This experiment is not as critical as it should have been because the pH of protamine may range between pH 2.5 and pH 10 and was not completely controlled. It is, however, suggestive.

On the basis of these and other studies, it does not seem inappropriate to indulge in speculation regarding the possibilities of the relation of such forces to the prevention or the acceleration of the clotting process. Does the presence of the negative zeta potential of a normal vessel

wall tend to repel the components of the blood, hence inhibiting the initial steps of clotting? This work has shown that, at least within certain limits, the anticoagulants tested increased the negative charges which encourages repulsion. Fibrinogen, which is essential to clotting, tends to counteract this tendency toward negative charges, thus decreasing repulsion. If the original observations are valid, protamine can counteract the action of heparin in this regard. Does this hold as well for individual molecules, and for other surfaces such as platelets? If so, it may explain the action of these substances, including the effect of these anticoagulants in decreasing the adhesiveness of platelets. Lloyd Wood has calculated that the electric double layer interaction may give rise to a repulsive force of such magnitude that the zeta potential may be a critical factor in preventing fibrinogen molecules from making contact.

This discussion must not be interpreted as indicating that physical factors, including electrical charges of repulsion and attraction, have been conclusively established as playing a significant role in blood clotting. Much work must be done before final evaluation of their significance will be possible. It was included in order to introduce a new method of approach to this problem, and to render less acceptable the opinion that the present conceptions of blood clotting represent the full picture of the clotting mechanism as it may be revealed ultimately. The physical chemist may well explain many of the enigmas of this complex system.

Morphologic Factors

The classic description of the thrombus begins with the attachment of platelets to the vessel wall—usually at the site of some damage to the intima—and thereafter develops with a white head made up of agglutinated, fused platelets and leukocytes. These are rendered adherent by sticky fibrin. Propagation of this thrombus proceeds with the accumulation of red cells together with the other components above mentioned. This picture is well known and requires no further comment. During recent years, however, certain additional findings have been recognized as having significant influence in the development of thrombi.

Stasis and Sludging

Under certain conditions stasis becomes an important factor in the development of thrombi. Patients who remain in bed are found to develop multiple thrombi, especially in the small vessels along the posterior aspects of their legs where pressure and stasis are marked.

Whether the process of sludging, which has been recognized for 100 years (Coccius, 1852) and which has been so intensively studied recently by Knisely,[1a] plays a major role in the development of these thrombi is not conclusively proved, but there is a distinct possibility that it may in some instances.

Students of blood flow in vivo have observed that *normally:*

(1) Circulating red cells not only do not agglutinate, but tend to repel each other slightly.

(2) No white or red blood cells adhere to the inner surfaces of small vessels which are smooth and clean.

(3)The flow of unagglutinated blood is laminar. In small arteries and veins the blood cells move in the axial stream surrounded by a concentric layer of plasma. The cells in the center of the stream move most rapidly. The platelets, being the lightest elements, usually move nearest the vessel walls and, while normally they are not in contact with the wall, disruption results in their being the first to contact the wall and usually the first to adhere to it.

(4) In larger vessels the normal rate of flow is rapid, but as the peripheral arterial vessels progressively narrow to the size of the arteriole and finally to the size of the capillary the rate of flow tends to slow.

In a variety of diseases, according to Knisely, clumps of agglutinated (sludged) blood may enter these progressively narrowed vessels and, in some instaces, permanently plug them because the cells fail to separate and pass through individually. Such permanent plugs have been seen in the terminal arterioles of the bulbar conjunctiva of the eye.

Observations of vessels in the horizontal

plane show that under conditions of slow or uphill flow, and in the presence of trauma and disease, the cell masses may settle along the lower side of vessels much as sediment settles in a pipe. Such cells may become cemented and firmly attached to the wall of the vessel, initiating a thrombus. As Knisely points out, there is probably a critical speed for each vessel which is necessary to keep cells moving along in the axial stream and below which they tend to settle out in masses. Whether these masses stick to each other depends on numerous factors, probably including the presence of fibrin, an injured vessel wall, anticoagulant therapy, and possibly the degree of repulsive electrical charges present.

The importance of anticoagulant therapy under such circumstances has been demonstrated by the experiments of Laufman, Martin and Tanturi.[22] These workers almost consistently produced sludging which developed into thrombi within 30 minutes after temporary ligation of the portal or superior mesenteric veins in dogs. In the control animals, when the occlusion was released the thrombi remained fixed in place. They concluded that thrombosis in these small vessels consisted of four stages: (1) the formation of sludge; (2) the adherence of the sludge masses to the endothelium; (3) the aggregation of more cells to the agglutinated mass; (4) the complete cessation of flow through the involved vessel when it had become entirely occluded by the agglutinated mass.

In contrast, when the dogs were heparinized or dicumarolized, release of the occlusion resulted in the breaking up of the sludge and the movement of the cells along in the vessels. Thus adhesiveness had been prevented by the anticoagulants.

Platelet Adhesiveness

The importance of platelets in the formation of a thrombus has been recognized since 1882,[23, 24] but only within the past few years has serious attention been paid to the mechanism of their function. Apitz,[25] M. B. Zucker,[26] and Howard Zucker[27] have made observations on the hemostatic action of platelets in vascular wounds and have shown that in vessels from 8 to 250 microns in diameter the occlusion of an opening in an injured vessel is almost entirely produced by platelets, which normally begin to appear within 10 to 30 seconds and become hemostatically effective within four minutes. They believe that there is no adequate evidence that fibrin plays a significant role in platelet thrombus formation although they admit that occasional strands of what they believe to be fibrin may be present. Platelet thrombosis plays no role in idiopathic thrombocytopenia.

The adhesiveness of platelets has been studied in considerable detail by H. P. Wright.[28] In postoperative and puerperal periods the circulating platelets *may rise to two or three times the usual number* and then return to normal; the incidence of thrombosis is highest during the increase of platelets. Helen Wright has now also demonstrated that *the adhesiveness of platelets increases during the same period* reaching the maximum adhesiveness between the sixth and tenth postoperative days. She has also demonstrated that the use of the anticoagulants heparin, dicumarol and Tromexan markedly reduce the adhesiveness of platelets, another step in understanding the mechanism of their effectiveness.

Spooner and Meyer[29] and Eisen and co-workers[30] have confirmed the effect of dicumarol on the reduction of platelet adhesiveness. The latter workers, using the method of Moolten and Vroman,[31] found platelet adhesiveness to be increased in thromboangiitis obliterans and thrombophlebitis in their active phases, but not in arteriosclerosis obliterans. They could not confirm the findings of Moolten and Vroman of an increase in platelet adhesiveness with coronary thrombosis. Eisen and associates reported that cigarette smoking did not increase platelet adhesiveness in normal subjects or in patients with arteriosclerosis obliterans but did increase the adhesiveness in patients with thromboangiitis obliterans. This was thought to be due to the activation of this disease associated with smoking. With cessation of smoking there was a significant decrease in platelet adhesiveness. If these findings can be confirmed, they add to our knowledge of this disease.

Whereas it was formerly believed that the

surfaces of platelets were dependent entirely upon the nature of their surrounding medium, the work of H. P. Wright and others has shown that under certain conditions the products of platelet activity probably escape through the surface of these platelets and the cell-plasma interface becomes covered with a film of fibrin. This adhesive surface contact film has such viscosity that even though two adherent particles may have a like electric charge their mutual repulsion may not suffice to overcome the cementing action of the viscous cementing film.

In addition, the hydrophilic colloids, which are increased in the blood postoperatively, act by reducing the surface charges on the cells and by modifying the positions of the adsorbed water on the cell surfaces. The cells are then enabled to approach each other more closely and, because their electrokinetic potentials are reduced, their surface tension is sufficiently great to overcome their mutual repulsion and aggregation may take place.

Fibrinogen and globulin are potent hydrophilic colloids in this regard, and it is possible that the increased tendency for platelets to adhere during the postoperative period is partly due to the increase in these substances.

The Relationship of Malignancy to Thrombosis

The Resistance of Thrombophlebitis on This Basis to Anticoagulant Therapy. The importance of phlebitis as a possible sign of obscure malignancy was pointed out by Trousseau[32] approximately one century ago. At times this may be migratory in nature involving veins in any area of the body. Often the malignant growth is not found until autopsy, when the relationship becomes clear. The site of origin is frequently in the pancreas, but malignancy in many—perhaps any—other organs may also be responsible. In our experience carcinoma of the pancreas responsible for thrombophlebitis may be located in any section of the organ, not necessarily in the body or the tail. Before the use of anticoagulants such thrombophlebitis was usually persistent until the death of the patient. The significance of the resistance to anticoagulant therapy of phlebitis associated with malignancy has not been fully appreciated to date.

Our own experience with the use of anticoagulants in such patients during the past decade appears to justify the following statements:

(1) While anticoagulant therapy may be effective in causing the subsidence of phlebitis during the early stages, as the malignant disease progresses the phlebitis may "break through" the anticoagulant therapy and persist despite it.

(2) The coumarin compounds seem less effective than heparin in combating this condition. There are, however, some cases in which heparin is less effective than the coumarin compounds. In the later phases, no anticoagulant is effective.

(3) The diagnosis of malignancy must be suspected: (a) whenever thrombophlebitis persists or is migratory in spite of adequate anticoagulant therapy in adults over 30, and with increasing suspicion in the older age groups; (b) whenever there is unexplained bleeding with prothrombin times in the therapeutic (not excessive) range.

We have now found cancer in 20 patients in whom it had been unsuspected until the significance of one of these findings was recognized. Even after our suspicion has been aroused, the malignancy has frequently been found only at operation or autopsy. The most common sites of origin have been pancreas and liver. Other sites have included the lungs, stomach, breast, rectum and uterus.

We are now becoming more inclined toward exploratory laparotomy in the presence of persistent phlebitis with negative x-ray and blood studies. The last two cases of silent carcinoma of the pancreas encountered have shown as their single abnormal blood finding progressive elevation in the serum alkaline phosphatase. In these, liver metastases were present.

The explanation for the initiation of the thrombosing tendency in these patients is not as yet understood. It has been held that it may be associated with release of an excessive amount of thromboplastin due to destruction of tissue cells, but there is no conclusive evidence of this. Other studies of the blood have been unrevealing. It is known that these areas

of migratory phlebitis are not typically metastases because:

(1) Areas which have been involved may clear up completely as the phlebitis migrates elsewhere.

(2) When the original cancer is removed completely (as with a hysterectomy for carcinoma of the uterus) the phlebitis frequently subsides.

(3) Pathologic studies usually fail to reveal any malignant cells in the thrombophlebitic lesions.

This *syndrome of resistance to anticoagulant therapy of thrombophlebitis associated with malignancy* is stressed for two reasons: (1) to alert clinicians to the possible significance of such a phenomenon; (2) to stimulate investigators

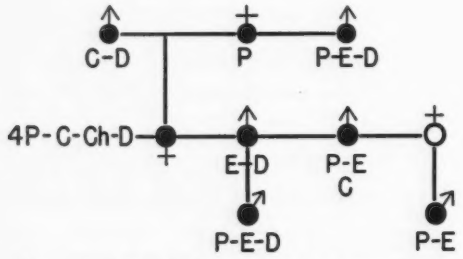


FIG. 10. Familial thrombosing tendency. Patient E. M., female, at left of second line (4P-C-Ch-D). P = phlebitis, E = embolism, C= coronary occlusion, Ch = Chiari's syndrome, D = dead from thromboembolism.

to seek the explanation either in the constituents of the blood, the new growth, or the local phlebitic area.

FAMILIAL THROMBOSING TENDENCIES

It appears that too little attention has been paid to what might well be termed familial thrombosing tendencies. It is probably more than coincidence when six or more members of the same family each develop from one to five thromboembolic conditions and when most of them eventually die of such conditions. We have studied several such families, an example of which is outlined herein.

The patient was a Jewish woman, 54 years old when first seen in 1946. Family history revealed the following (fig. 10):

(1) Her father died of coronary occlusion. (2) Her mother had recurrent thrombophlebitis with venous insufficiency for many years. She died of cancer. (3) One maternal uncle developed phlebitis and died of a subsequent pulmonary embolus. (4) The elder of the patient's two brothers suffered from a broken leg, phlebitis, and pulmonary embolism. (5) His son developed phlebitis after an appendectomy with a subsequent pulmonary embolus from which he died. (6) The patient's younger brother has suffered from phlebitis of the saphenous veins, has had pulmonary embolism and also coronary thrombosis, but he is still alive. (7) The patient's only sister has suffered from no thromboembolic conditions. (8) The sister's son, however, has suffered from phlebitis and has had pulmonary embolism, but is still alive.

Such a family history seems significant, especially when it is known that the history of the patient is even more complicated in terms of thromboembolic conditions.

In May of 1943, following hysterectomy, she developed bilateral femoral thrombophlebitis with multiple pulmonary infarctions from which she recovered very slowly. In November of 1944 thrombophlebitis recurred in the right leg. In April 1945 she developed the first of a series of serious coronary occlusions which kept her bedridden until September, 1945. In December, 1945 there was suggestive evidence of a mild cerebral thrombosis which affected sensation in the right arm. During the fall of 1946 a series of small thromboses occurred involving the veins of the right foot and hand. Long-term dicumarol therapy was advised but refused.

The patient did fairly well until March, 1948 at which time phlebitis was present in the superior superficial abdominal veins. Ascites was present and there was marked deep tenderness over the liver and spleen. The diagnosis of Chiari's syndrome was made and she was placed on dicumarol therapy. Her course, which had been steadily downhill, reversed, and she made steady improvement with diminution of the ascites and of the tenderness. She became ambulatory, but continued to have a moderately enlarged liver and spleen and some abdominal pain, especially in the left upper quadrant. She remained on dicumarol, with the prothrombin time maintained between 20 and 25 seconds, but became less meticulous about her treatment and the levels were not well controlled. Coincident with this, a reactivation of her process occurred and she entered New York Hospital with evidence of extensive liver damage and return of her ascites. Her course was rapidly downhill. She became jaundiced, stuporous and died on September 21, 1949.

Autopsy showed thromboses of the hepatic veins (Chiari's syndrome) and of other veins of the abdomen with hepatomegaly and splenomegaly.

Thus far studies of the blood clotting mechanism in such cases have failed to reveal a significant common factor. These studies have included clotting time, bleeding time, prothrombin time, fibrinogen studies and platelet counts. Some of these patients have shown shortened dilute prothrombin times, but the relationship appears inconclusive. Such families should be studied in much greater detail than heretofore. They may reveal information of the greatest significance regarding the clotting mechanism.

Clotting Tendencies in the Individual

Some persisting factors also appear to play a role in certain patients who, without a family history, continue throughout their lives to have recurrent thromboembolic episodes without a recognizable underlying disease. This has been described by Nygaard and Brown[33] under the name of essential thrombophilia, but too little attention has been paid to this phenomenon. For example, a young man suffered a minor injury which resulted in thrombophlebitis of the left saphenous vein. He recovered without incident, but five years later a thrombus formed in the saphenous vein of the opposite leg which released multiple pulmonary emboli. He survived, but during his life had four more attacks of thrombosis, finally dying at 44 of coronary thrombosis with myocardial infarction. His blood studies failed to reveal an abnormality of sufficient significance to explain this predilection toward thrombosis. Such cases are not uncommon, but the explanation is unknown.

Experience with both the familial and the individual thrombosing tendency has emphasized the fact that the present tests for clotting factors are still inadequate. It is not sufficient to label these syndromes with names without understanding the mechanism responsible for them.

Cryoglobulinemia

Among the more interesting conditions which may simulate thrombosis but concerning which there is no evidence thus far that the true mechanism of thrombosis is involved are cryoglobulinemia and the syndrome of cold hemagglutinins. In both of these syndromes the blood may become thickened to the point of obstructing, interfering with the circulation through the minute vessels, producing secondary infarction and, in severe cases, gangrene of the tissues.

The cold, precipitable proteins of cryoglobulinemia[34–36] are encountered most commonly in multiple myeloma and kala-azar, but may also be encountered in the presence of arthritis, hepatic disease, disseminated lupus and rarely with other diseases. They may be present in some, but not the majority, of patients with the Raynaud's syndrome.

While the occurrence of cold precipitable agglutinins in the serum or plasma is not a very rare phenomenon, the presence of clinically significant amounts has only been recognized in about 15 cases.

Of importance in our present discussion are the following observations. Characteristically there is difficulty in withdrawing blood samples and carrying out procedures with the blood, because when the temperature of the blood falls below 37 C. the cells agglomerate and become enmeshed in a precipitate of cryoglobulin. Warming to above 37 C. generally produces resolution of the precipitate and freeing of the cells. While the temperature of the central areas of the human body (e.g., rectum) tends to remain above 37 C., it is not uncommon for the temperatures of the peripheral and superficial areas to fall far below this critical point upon exposure to low environmental temperatures or such common acts as handling of ice. It is not surprising, therefore, that under such circumstances, sludging, precipitation and obstruction of the vessels may occur. If this persists over long periods of time, infarction and gangrene may result. In one case to be reported by Dr. David Barr the tissue damage was of such an order that gangrene of the fingers, toes, nose and ears occurred. (Figures 11*A* and *B* are shown through his courtesy.)

Cold Hemagglutinins

Cold hemagglutinins have been reported in low titer in the serums of patients with a great variety of diseases and in normal individuals. These agglutinins which are found in human serum characteristically act specifically on sensitive cells of the patient or of

other individuals. This reaction of clumping of the cells is precipitated by cold, even at room temperature, and reversed by warming to body temperature. The first report of gangrene produced by the obstructive action of cold hemagglutinins appeared in 1937.[37] Since that time other reports of gangrene of the extremities on this basis have appeared.[38–41] In several of these cases hemolytic anemia accompanied this phenomenon.[39, 40]

The obstruction appears to be on the basis of mechanical blockage produced by masses of cells in clumps and rouloux, acting much as log jams as the arterial tree becomes progressively narrower. No cryoglobulins are involved, although doubtless these two conditions and

FIG. 11*A*. Cryoglobulinemia with secondary gangrene of the fingers. From Medichrome Series, M. M. Vascular Diseases, I. S. Wright and W. T. Foley. (Courtesy of Dr. David Barr.)

FIG. 11*B*. Cryoglobulinemia with secondary gangrene of the toes. From Medichrome Series, M. M. Vascular Diseases, I. S. Wright and W. T. Foley. (Courtesy of Dr. David Barr.)

thrombosis in the classic sense have been confused in the past. The agglutination produced by cold hemagglutinins does not involve the constituents of the blood in the true thrombosing process. Mere warming of the part or the test tube reverses the process, although if ischemia of tissue has persisted for a sufficient length of time the stages of necrosis will proceed with loss of tissue.

The Influence of ACTH and Cortisone on Blood Coagulation

It was to be anticipated that certain patients receiving ACTH or cortisone therapy would develop thromboembolic conditions on the basis of their underlying diseases and other associated factors, such as dehydration and complete bed rest. Many of the diseases for which these drugs are given are serious, many involve the cardiovascular system, and a fairly high percentage of the patients are in the middle or older age groups. Considerable caution must therefore be exercised before attributing any specific thromboembolic episode occurring during or shortly after ACTH or cortisone therapy to these drugs.

Nevertheless, experience appears to indicate that the incidence of thromboembolic complications may be increased by their use. This possibility has been confirmed by the demonstration of changes in the clotting mechanism associated with their administration. Cosgriff, Diefenbach and Vogt[42] have reported 11 thromboembolic episodes, including two deaths from pulmonary embolism, which occurred among 175 patients who received ACTH or cortisone for varying lengths of time, but they failed to include figures on the incidence of similar complications in a series of patients with the same groups of diseases followed over comparable lengths of time but not receiving these specific drugs. At the New York Hospital we have observed thrombosis occurring in four such cases recently. The underlying diagnoses were sprue, ulcerative colitis, nephrosis, and pemphigus. These do not, however, constitute observations of statistical significance.

Of perhaps greater significance was the finding by Cosgriff and co-workers[42] that 8 of 10 patients tested showed considerable shortening of their coagulation time* while receiving ACTH (five patients) or cortisone (three patients). Four of six individuals showed a marked decrease in the heparin-retarded coagulation time† while receiving ACTH.

No consistent or significant changes were noted by these observers in the results of tests for prothrombin time, fibrinogen B, or protamine titration.

R. W. Smith and his co-workers[43] have also examined this matter. They concluded that the adrenal cortex may shorten the clotting time during therapy. Additional studies included prothrombin time with whole and diluted plasmas, two-stage prothrombin studies, antifibrinolysin, Ac-globulin and protamine titer. The results of these studies appear to have varied widely and cannot be regarded as conclusive.

To date, therefore, no definite explanation for the shortened coagulation time has been determined, and this must await further studies. These observations raise the question of whether anticoagulants should be used prophylactically in appropriate cases, such as those with vascular disease and marked debilitation and those on a regimen of prolonged bed rest. The usual contraindications to anticoagulant therapy should, of course, be observed.

Combatting Thrombosis

A successful attack on thrombosis requires (a) prevention of the original development, (b) prevention of propagation or multiplication of any already formed thrombus, (c) prevention of the delivery of embolic offspring, and (d) encouragement of the dissolution of the original thrombus.

These objectives have been easily attainable in a test tube by the use of anticoagulants. Their attainment in man, however, has been fraught with difficulties for the physician and risks for the patient. Technics have now been evolved by means of which *conscientious physicians* with the aid of *accurate technicians* can reduce the death rates and the incidence of complications from thromboembolic diseases to a significant degree. In spite of the improve-

* Lee-White technic.

† Waugh-Ruddick modification of the Lee-White technic.

ment in therapeutic results which may be obtained by the use of heparin, dicumarol, Tromexan, Paritol, phenylindanedione and 4-hydroxycoumarin No. 63 (Link) (B. L. 5), the following qualifications must be included in any evaluation of these drugs:

(1) There are some failures with each anticoagulant. Patients may develop thromboembolic complications despite the maintenance of so-called "therapeutic levels" of clotting or prothrombin times. The incidence of these complications is, however, significantly lower than in comparable control series.

(2) Uniform response to a given dose cannot be obtained in all patients and no drug thus far available is an exception to this statement. Even heparin and Paritol administered intravenously may produce results that vary considerably. As is to be expected, drugs dependent upon intestinal absorption and utilization show a wide range of response.

INVESTIGATORS	Number of Cases		Mortality Per Cent		Thromboembolism Per Cent	
	Control	Treated	Control	Treated	Control	Treated
COMMITTEE ON ANTICOAGULANTS-A.H.A.	442	589	23.4	16	26(42)*	11 (13)*
PETERS, BRAMBEL (1) MERCY – Baltimore	86	110	25	11	15	1
PARKER, BARKER (2) MAYO CLINIC	100	50	13	10	37	4
NICHOL, PAGE (3) JACKSON – Miami	0	44	--	16	--	2
GREISMAN, MARCUS(4) LINCOLN – N.Y.	100	75	35	9	21	4
PRESTON TAYLOR (5) ROOSEVELT – N.Y.	54	45	22.5	20	25	10.6
ZELUFF, FIELD (6) BELLEVUE – 1st Div.	100	80	40	25	20	5
SMITH, KEYES, DENHAM(7) HENRY FORD – Detroit	731	189	25	14	19	8
SCHILLING (8) ST LUKES – N.Y.	60	60	40	17	25	5
TOTAL (2915)	1673	1242	25.7	15.3	22.1	8.1

NOTE-- 1. Identical trends in each series
2. Confirmation of A.H.A study by others separately and collectively

* Number of thromboembolic complications per hundred patients

FIG. 12. Coronary thrombosis. The effect of anticoagulants on the mortality and thromboembolic complications.

(3) The use of any anticoagulant is attended with a certain risk of hemorrhage. Even though the drug is administered with great care, a silent ulcer or cancer, or some other obscure process, may start to bleed when the natural protective process of clotting is altered.

Since there have been many reports of the actions, problems and the clinical results following the use of heparin and dicumarol, no attempt will be made to review this literature. These drugs have made it possible to establish beyond doubt the great importance of anticoagulant therapy. They have also contributed significantly to the knowledge of the phenomena involved in blood clotting.

Specifically, the use of anticoagulants has been clearly established as the treatment of choice in the great majority of cases of *thrombophlebitis, with or without embolic episodes.*[44–48] There is considerable evidence to show that the use of these drugs postoperatively for prophylactic purposes will reduce the thromboembolic complications significantly.[49–51] There is some question at present whether their use is justified in every surgical case or merely in selected cases such as those involving pelvic or massive surgery where there is a high risk of thromboembolism. The development of more simple methods of anticoagulant therapy may answer this question.

Patients with *rheumatic heart disease with fibrillation and multiple embolization* should be kept on ambulatory anticoagulant therapy to prevent continued propagation of the mural thrombi and continued embolization.[52–55] The risk is markedly reduced if therapeutic levels are maintained. For this and other long term therapy the coumarin compounds appear more satisfactory, and they are much less expensive than heparin.

The use of anticoagulants in the treatment of coronary thrombosis with myocardial infarction has been the subject of intensive study during the past few years, and the reports of the Committee on Anticoagulants of this Association have been published. The final results, soon to be published, completely confirm the progress reports. Numerous other reports have been confirmatory to a remarkable degree.[56–63] (See fig. 12.)

Recently a report appeared by Russek and his associates[64] suggesting that it is unnecessary to give anticoagulant therapy to mild cases of coronary thrombosis because the death rate and the complication rate is so low in these cases. If one could *inevitably* foresee which patients will develop a mural thrombus with emboli, or a thrombosis in a vein of the leg, with subsequent pulmonary emboli, or other thromboembolic complications, this might be an acceptable position. Unfortunately, experience is replete with numerous examples where such prophetic foresight has failed. It is more difficult to predict

whether the course of a case will be mild or severe on the day of onset, when decisions regarding therapy must be made, than in retrospect, after the patient has been discharged from the hospital. If a physician waits until the first thromboembolic episode occurs, he may have a permanently disabled patient, as in the case of hemiplegia due to an embolus to the brain, or even a dead one.

In some institutions (usually private hospitals without a city ambulance service) the incidence of death and complications is lower than in most other hospitals. Such hospitals may have a lower incidence of patients who are extremely ill at the time of admission. It is also doubtless true that many very mild cases are cared for in the home, or, indeed, may not be recognized at all. This has resulted in reluctance on the part of some physicians to use anticoagulants. (See fig. 13). Because the sequelae and thromboembolic complications of myocardial infarction are so serious, it appears only reasonable that *the risk should be reduced to the minimum* by the use of all available therapeutic measures If these patients are to receive the maximum benefit that modern medicine affords, they should receive anticoagulant therapy provided that:

(1) There are no contraindications to anticoagulants which would produce too great a risk. These contraindications may include difficulties in local arrangements as well as complicating diseases in the patients.

(2) The physician knows how to use anticoagulants and is willing to observe the necessary meticulous care.

(3) Accurate facilities for clotting time or prothrombin time tests are available, depending on the anticoagulant used.

If these criteria are fulfilled, the risks of anticoagulant therapy are very low indeed. During the past 10 years the author has supervised the anticoagulant treatment of more than 2000 patients, several hundred of whom have been under ambulatory therapy for from six months to five years. During this extensive experience not a single one of these patients under our direct control has died of hemorrhage due to anticoagulant therapy. There were hemorrhagic episodes, some serious, during the early experimental years, but, by the combination of careful observation, prompt treatment, and perhaps good fortune, no deaths occurred. This record is paralleled closely in many institutions where the program is carried out seriously. It is mentioned merely to demonstrate that *the risk is not excessive under proper conditions.* The risk is increased under unfavorable conditions, and the physician must always weigh the risk of the disease against the risk of the therapy, taking all factors into consideration.

There is accumulating evidence that the *use of anticoagulants in patients with congestive heart failure* is sound and results in decreased or delayed mortality and decreased thromboembolic episodes.[65,66] Each case in this group must be evaluated in relation to the indications for anticoagulant therapy.

Number of cases*	*THROMBOEMBOLIC COMPLICATIONS*
12	VENOUS THROMBOSIS
12	PULMONARY EMBOLISM
7	PERIPHERAL EMBOLISM
3	CEREBRAL EMBOLISM
1	Extension of a MYOCARDIAL INFARCTION
35**	

* Listed according to the last complication prior to the institution of anticoagulants therapy.

** Of these 35 cases
22 received anticoagulants after their first complication,
9 received anticoagulants after their second complication,
3 received anticoagulants after their third complication,
1 received anticoagulants only after his fourth complication.

FIG. 13. Thromboembolic complications which caused patients to be placed on anticoagulant therapy; A.H.A. study.

The use of anticoagulants has also been advocated in a wide variety of other conditions involving thrombosis, but the available evidence is as yet less conclusive than in those mentioned above.

Most of these early studies have been conducted with heparin or dicumarol, or both.

A few words should be said about the newer anticoagulants now under study.

NEWER ANTICOAGULANTS

Tromexan

3,3′-Carboxymethylenebis (4-hydroxycoumarin) ethyl ester has been used extensively in Europe and more recently in this country. Although Overman and his associates[67] had

investigated the acid in 1940, they did not take the next step of esterification.

Early reports of von Kaulla,[68] and von Reinis and Kubik[69] (1948) stated that the oral administration of Tromexan produced a rapid increase in the prothrombin time which reached a maximum response in 12 to 24 hours following a 900 mg. dose. The return to normal was also relatively prompt after cessation of the drug.

into the vein of a rabbit's ear, which remained relatively permanently (fig. 14) in the absence of anticoagulant therapy would be cleared away in a few weeks when the rabbit received Tromexan (fig. 15). This is thought to be due to fibrinolysin and other enzymes in the blood which act with greater effectiveness when the clot-forming elements of the blood are rendered less effective by the presence of anticoagulants.

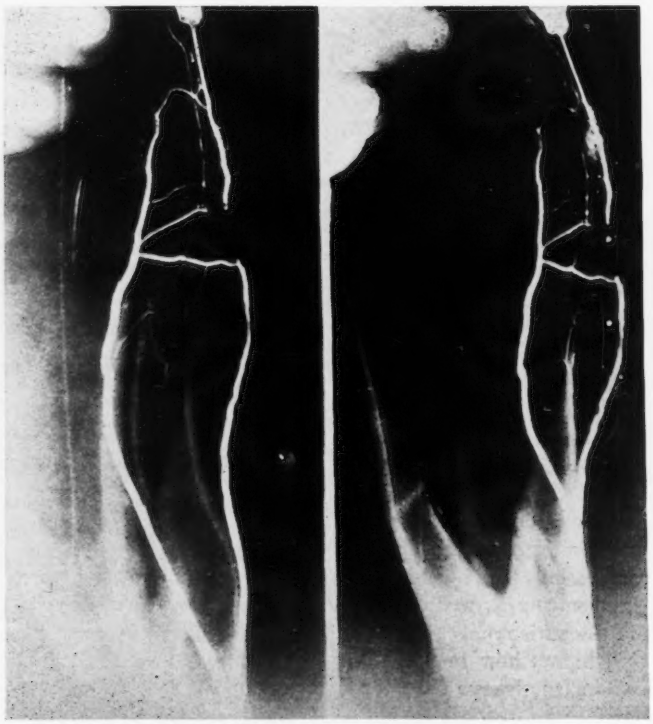


FIG. 14. Occlusion of vein of rabbit's ear after injection of sodium morrhuate. Control. *Left:* initial. *Right:* six weeks later, vein still occluded. (Courtesy of Dr. H. P. Wright.)

Numerous other workers in Europe have generally confirmed these findings.[70–74] Helen P. Wright, Burt and Kubik[75] in England also reported experiences with Tromexan in the treatment of 126 patients with thromboembolic disease. In addition, these workers have demonstrated that the use of coumarin derivatives (Tromexan was actually used) do exert a definite effect on a thrombus which is already formed. They showed that a thrombus produced by the injection of sodium morrhuate They also reported that in over 80 per cent of their cases the prothrombin activity decreased at least 50 per cent within 36 hours and returned to normal within the same period after discontinuance of the drug.

Burke, working in our laboratory, carried out studies on rabbits standardized according to the technic of Overman, Stahmann and Link.[76, 77] As previously reported,[78] 400 mg. of Tromexan produced a fairly consistent prolongation to about double the control prothrombin time in

from 18 to 24 hours. The average peak of action occurred in 30 hours. Twenty-four normal human subjects were then tested with doses of 1200 to 1500 and 1800 mg. of Tromexan. Within 24 hours these individuals showed a prolongation of their prothrombin times to 20 to 30 seconds (undilute plasma) and 65 to 100 seconds (dilute plasma). This series of normals showed a fairly uniform response. While this was more rapid than that experienced with dicumarol, nevertheless, both the initial measurable rise and the maximum levels attained were found to be slower than those reported by von Kaulla, and von Reinis and Kubik.

Continued experience with Tromexan, which now includes cases of thromboembolic states, has confirmed the finding that in the majority of patients following the administration of 1500 to 1800 mg., the increase of the prothrombin time to 20, 25 and 30 seconds is more rapid than following the administration of dicumarol (fig. 16). However, as in the case of all drugs, especially those administered orally to ill patients, the rate of action does not follow an exact and predictable curve. Some patients appear resistant to Tromexan and show a retarded response. This has been a more serious problem with dicumarol with its even longer lag in action. Occasionally a patient who has been maintained in a good therapeutic range may suddenly develop a rise of the prothrombin time to 60 or more seconds. This appears to be more common with Tromexan than with dicumarol, but merely omitting one or two doses will almost uniformly result in a return of the prothrombin time to a safe level within 24 to 36 hours. Of 263 cases from six hospitals participating in the cooperative study of the American Heart Association, all except 17 had shown a definite decrease in the prothrombin time within 36 hours after ceasing the administration of Tromexan. Of these, five remained at

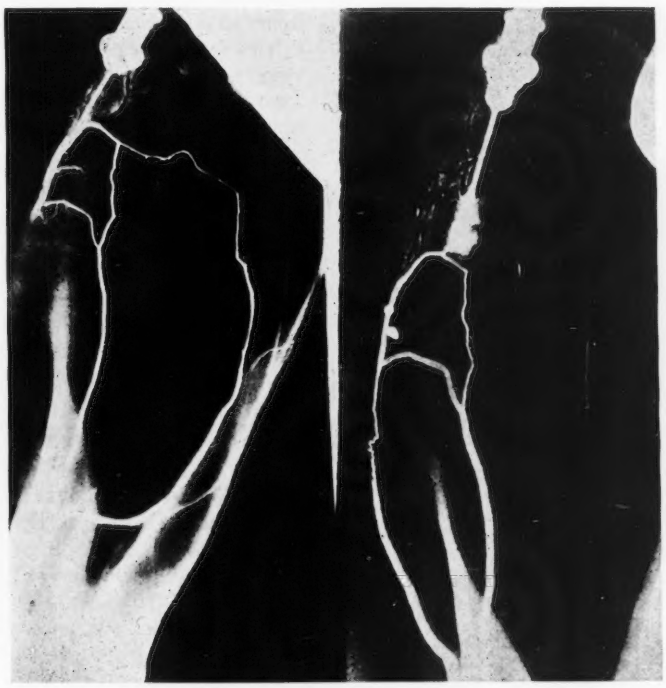


FIG. 15. Clearing of occlusion produced by sodium morrhuate when rabbit received Tromexan. *Left:* initial occlusion with thrombosis. *Right:* three weeks later; vein clear. (Courtesy of Dr. H. P. Wright.)

the same level and 12 showed a rise. (Five had received two large doses the previous day; in two the time rose only 1 to 2 seconds; one was hypersensitive; two had renal disease; and two were unexplained.) Figure 17, compiled by Dr. Louis Scarrone of our laboratory, illustrates a comparison of a study of 50 cases after Tromexan and 52 cases after dicumarol.

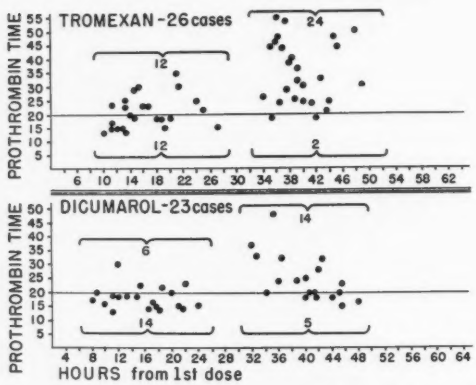


FIG. 16. Scattergram showing the relative rates of prolongation of the prothrombin time after 1500 to 1800 mg. of Tromexan, plus 900 mg. the second day, and 300 mg. of dicumarol, plus 200 mg. the second day. Compiled by Dr. Louis Scarrone.

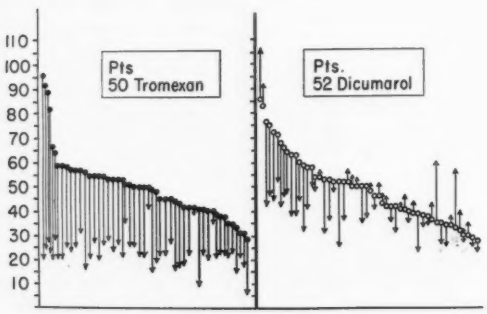


FIG. 17. Extent and direction of change in prothrombin time within 36 hours after last dose of Tromexan and dicumarol. No vitamin K or transfusions were given. In every instance following the termination of Tromexan the trend was downward to safe levels. Thirty-six hours after the termination of dicumarol 19 out of 52 patients showed prothrombin times which were still higher than the previous test. Compiled by Dr. Louis Scarrone.

Rosicky,[73] originally working on the premise that slowness of absorption of dicumarol played an important role in its delayed action, weakened the methylene linkage between the two coumarin groups by adding the carboxyl radical. The work of Hausner and co-workers[79] in which dicumarol and Tromexan were labeled with C^{14} and the absorption from the intestinal tract studied, does not seem to indicate that the difference in their rate of action depends on this factor. It appears that it may rest on the more rapid and intense accumulation of Tromexan in the liver. Their work did confirm the finding of more rapid action of Tromexan.

In our experience, following an initial dose of 1500 to 1800 mg. most patients are controllable with doses of 300 mg. two or three times daily, depending on the requirements of the patients. Occasional patients may require 1200 mg. a day during the acute (hyperprothrombinemic) phase of their illness. Rarely a very sensitive patient requires only 300 mg. a day. In other words, Tromexan is about one-fifth as active as dicumarol. Daily prothrombin time determinations are necessary at first, but after one or two weeks these may be separated more widely. We are now carrying an average of 40 or more patients on an ambulatory regimen with Tromexan controlled by weekly prothrombin determinations. Some physicians have reported informally that they have had greater difficulty in controlling Tromexan than dicumarol. This may be, at least in part, due to greater familiarity with the latter drug. Other factors include the use of single rather than divided daily dosage and the greater lability of response to the drug.

All anticoagulants must be regarded with respect since they may encourage serious bleeding, and Tromexan is no exception to this general rule. If a patient is on dicumarol therapy and has shown daily prothrombin time of 30 to 45 seconds, and if one day this increases to 70 seconds, no one can predict whether on the following day the prothrombin time will be lower or higher, unless vitamin K or transfusions are administered (fig. 18). It may be markedly higher and it may remain so for several days. Furthermore, the longer it remains elevated, the greater is the risk of serious bleeding. If, while using Tromexan, the prothrombin level reaches 70 seconds, merely dis-

continuing the drug will almost invariably result in a return well toward normal within 24 to 36 hours without either vitamin K or transfusions (fig. 19). As a result of this, the use of vitamin K or transfusions is very rarely required. (See fig. 20.)

The exact mechanism responsible for the more rapid decrease in the effects of Tromexan is not fully understood, but the work of Hausner and co-workers[79] with C^{14}-labeled coumarin derivatives does demonstrate that this is associated with a more rapid fall in body retention paralleled by a higher urinary excretion rate in the first few hours after oral administration. Very exceptional patients have been encountered in whom an elevation of the prothrombin time has persisted for several days after discontinuing Tromexan.

Phenylindanedione (Danilone, P.I.D.)

In 1944 Kabat, Stohlman, and Smith[80] described the effect of certain indanedione derivatives on prothrombin levels in animals. Soulier and Guegen[81] (1947) reported the use of phenylindanedione clinically as an anticoagulant. Jaques[82] stimulated further interest in this substance by demonstrating that its effect on the prothrombin time was more prompt than that of dicumarol. He also found that vitamin K is not effective in counteracting the action of this drug.

Blaustein and his co-workers[83] have recently reported clinical experience with phenylindanedione. They found that the most satisfactory initial dose was 200 mg. given orally for those patients weighing 150 pounds or more and 150 mg. for lighter patients. Following this dose a satisfactory therapeutic level (approximately 30 per cent of normal prothrombin activity) was reached in 38 out of 53 patients within 36 to 48 hours (figs. 21, 22). In 18 of these the therapeutic level was reached within 20 hours. In a few, however, there exists practically a complete resistance to this drug (fig. 23). In a series of 200 treated with phenylindanedione Blaustein has encountered 10 such patients.

This may represent a serious problem. With all coumarin derivatives relative resistance may be encountered, but some anticoagulant effect is usually noted with the prothrombin time test performed with 12.5 per cent plasma even with a delayed rise when the whole plasma test is used. With phenylindanedione, however, valuable time may be lost before its ineffectiveness is recognized.

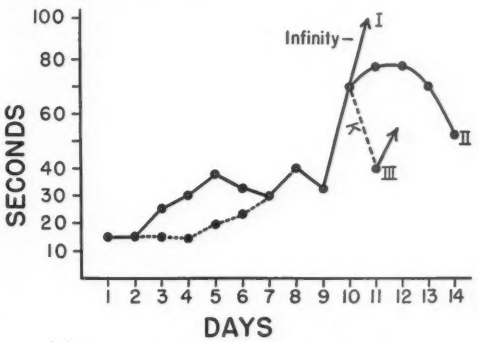


FIG. 18. Composite dicumarol curves.

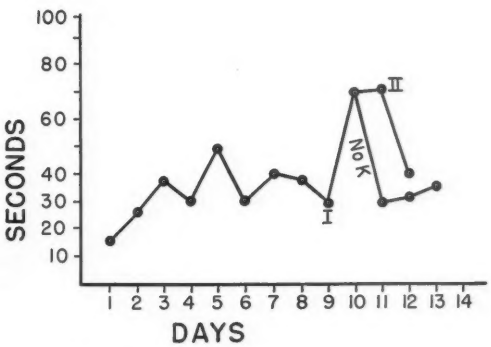


FIG. 19. Composite Tromexan curves.

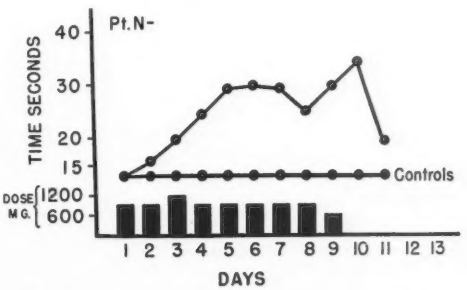


FIG. 20. Tromexan therapy (conservative). Diagnosis: thrombophlebitis, right saphenous vein; severe hypertension.

Phenylindanedione quite frequently produces wide swings in the prothrombin time curve,

even to prothrombin times of infinity. Nevertheless, bleeding has been rare with this drug.

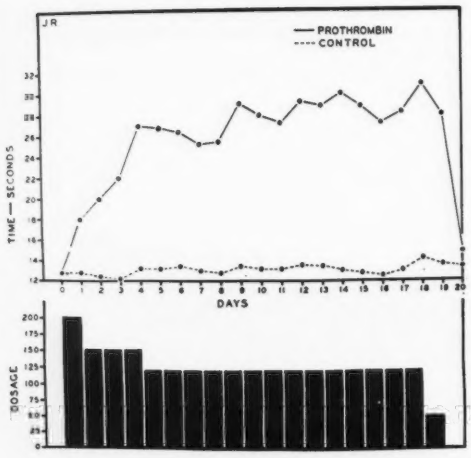


FIG. 21. Prothrombin time curve produced by phenylindanedione administered in single daily doses. (Courtesy of Dr. Blaustein.)

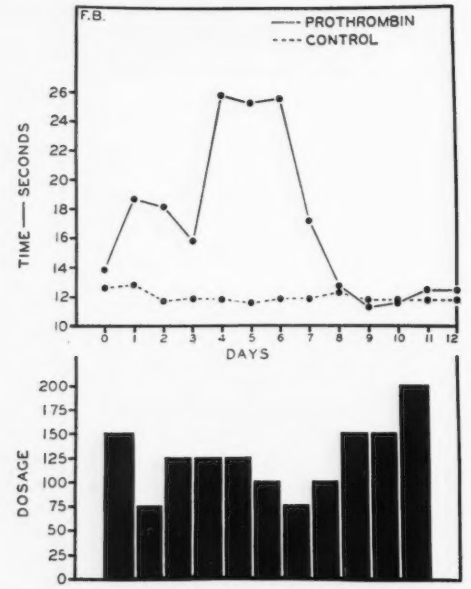


FIG. 22. Showing difficulty encountered in control of prothrombin time with phenylindanedione. (Courtesy of Dr. Blaustein.)

Divided doses totaling 50 to 150 mg. a day, depending on the requirements, result in a more stabilized curve.

Toxic effects thus far reported include mild hematuria and epistaxis. Renal damage (believed by Soulier and Guegen[81] to be due to deposition of crystals in the tubules), dryness of the mouth, polydipsia, polyuria and tachycardia, and scarlatiniform rashes have followed dosages as high as 10 to 20 mg. per kilogram per day, but have not been observed by Blaustein when proper doses were administered.

Phenylindanedione has the advantage of

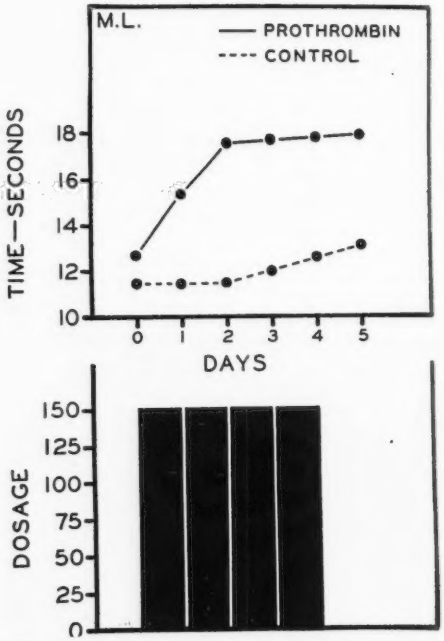


FIG. 23. Resistance to phenylindanedione. (Courtesy of Dr. Blaustein.)

rapid cessation of action after administration of the drug is stopped. The average time for return to normal of the prothrombin time was 48 hours. This factor is of considerable importance in view of the ineffectiveness of vitamin K.

Clinically the drug appears to be effective in the treatment of thromboembolic conditions, although a large series of cases has not been analyzed as yet.

At the present time phenylindanedione would appear to have the advantages of rapid onset and cessation of action to a degree comparable to Tromexan. The action, however, appears

less predictable and may extend all the way from complete ineffectiveness to extreme prothrombin times of infinity. Furthermore, the inability of vitamin K to counteract its effects makes its use hypothetically more hazardous.

4-Hydroxycoumarin Anticoagulant No. 63—B. L. 5 (2-methyl-2-methoxy-4-phenyl-5-oxodihydropyrano-(3,2-c) (1) benzopyran)

Compound 63 was synthesized by Ikawa working in Link's laboratory in 1942.[84] Early work with this substance was reported by Overman and associates[67] and Scheel, Wu and Link.[85] Battle and co-workers[86] have reported experience with it in dogs and in man. This coumarin derivative acts like dicumarol and Tromexan in that it depresses the prothrombin activity, but its rate and duration of action have certain characteristics. In dogs the administration of single doses even as high as 100 mg. per kilogram did not result in fatal hemorrhage, but daily doses of 5 mg. per kilogram killed six out of seven dogs within 30 days. While gross hemorrhage was the cause of death in these animals, the toxic lesions of small blood vessels previously reported by Meyer and co-workers[87] following lethal doses of dicumarol were singularly absent.

In man a single oral dose of 2 mg. per kilogram has been found, in most instances, to produce a desired therapeutic prothrombin time within 24 to 48 hours. This is somewhat more rapid than with dicumarol. The action of compound 63 is, however, much more prolonged. In 12 of 13 trials the prothrombin time remained elevated above the pretreatment level for an average of 8.75 days with extremes of 4 to 14 days. Hanson, Mann and Barker[88] have confirmed these findings. With this prolonged action daily doses would usually seem undesirable and a therapeutic level has been maintained on doses administered at two to five day intervals. With limited experience this substance appears to be relatively nontoxic and free from hemorrhagic manifestations in man, other than the risks inherent in all anticoagulant therapy. Nevertheless, it has not seemed wise, at least during the early stages of treatment, to omit daily prothrombin time tests in order to follow the activity curve.

At first thought, there would appear to be a distinct advantage in having an anticoagulant which needs to be administered only two or three times a week if its action were entirely predictable and if its action could be quickly terminated at any desired time, for example, when the necessity for an emergency operation arises. Barker[88] feels that the action of compound 63 is more consistent than that of dicumarol. Water soluble vitamin K is not very effective in bringing the prothrombin time back to normal levels, and if a decrease in prothrombin time is produced by this vitamin there is a strong tendency for it to rise to high levels again due to the persistent action of the drug. Vitamin K_1 in doses of 250 to 500 mg. has proved to be effective when given orally or parenterally.[88] This is not, however, generally available as yet, and, once administered, it may interfere with the action of coumarin compounds if it is desired to use them again within a few days.

Compound 63 appears two to three times more potent per unit of weight than dicumarol and 10 to 15 times more potent than Tromexan, but this is not of great importance because the total dosage of all of these drugs is well within the bulk easily taken by patients.

The final status of compound 63 has not yet been determined. Some observers may prefer this substance because of its more prolonged action. Further investigation of its properties appears justified.

Paritol

Paritol, a synthetic polysulfuric acid ester of polyanhydromannuronic acid, is similar to heparin in both chemical structure and action.

During the past three years studies have been carried on regarding its pharmacology, toxicology and clinical effects.[89–92]

Extensive clinical experience with this interesting material appears to justify the following conclusions. Paritol produces a significant prolongation of the clotting time when administered to man. By adjusting the dosage this can be in the same range as that following the administration of heparin. Paritol is about one-seventh as active as heparin when compared as milligrams of the drug per kilogram of body

weight. The duration of the anticoagulant effect of Paritol is from two to four times that of heparin (figs. 24, 25). Repeated doses of Paritol given at 8 to 12 hour intervals can produce a

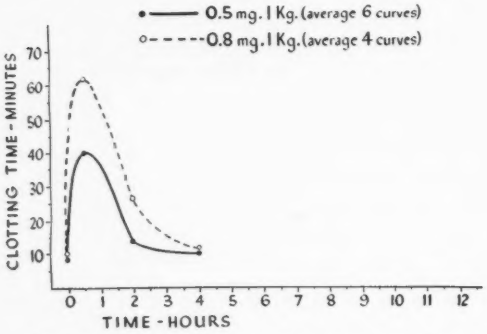


FIG. 24. Effect of intravenously administered heparin on the clotting time.

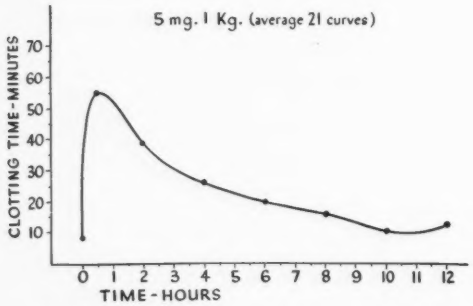


FIG. 25. Effect of Paritol on the clotting time.

Time after Paritol	Clotting Time Minutes	Prothrombin Time Seconds	
		100% Plasma	12.5% Plasma
Control	7	16	38
30 Minutes	57	23	47
2 Hours	32	22	41
4 Hours	15	17	39
6 Hours	14		

FIG. 26. Effect of Paritol on the prothrombin time.

satisfactory curve of the clotting time for anticoagulant therapy. The prothrombin time is also prolonged to a moderate degree in a range comparable to that observed with heparin therapy (fig. 26).

One would not be justified in recommending Paritol for general use at this time because certain adverse reactions have occurred in a number of patients. The most important of these has been a shock-like reaction, producing in some patients generalized vasomotor collapse. Additional adverse effects include urticaria-like reactions, elevation of the blood urea nitrogen in patients with renal disease, and the late development of alopecia. It should perhaps be recalled that the use of the early preparations of heparin was associated with some adverse and even severe reactions. If these actions can be eliminated, Paritol will represent an advance in that it is much less expensive to prepare and its action is more prolonged than that of heparin. The problem of the production of alopecia may be a very difficult one to eliminate. This complication has also be observed following the use of a related synthetic heparinoid known in Germany as thrombocid.

A Lipid Inhibitor of Blood Clotting

Among additional anticoagulants worthy of further study is the lipid thromboplastic inhibitor (antithromboplastin?) described independently by Overman[11, 13, 93] from our laboratory and by Tocantins.[14, 94] The inositol phosphatide fractions of rabbit brain and lung, of soybean and of plasma phosphatides have been found by Overman to contain the active component. These workers have injected this material into rats and rabbits without untoward effects. In vitro studies indicated that this is an active anticoagulation agent and that it acts against thromboplastin.

Coon, Flynn and Vassar[95] have recently reported effects of this lipid inhibitor in dogs. Their inhibitor was prepared as a 2 per cent emulsion from acetone dried beef brains. Varying amounts of this emulsion were injected intravenously into dogs without apparent untoward effects. Factor V, as measured by the method of Flynn and Standly, showed a prompt decrease, often as much as 75 per cent. The prothrombin levels as measured by the two-stage method also decreased as much as 70 per cent, depending on the amount administered. The one-stage prothrombin test appeared less sensitive, requiring larger doses to produce a

measurable effect. The effects on factor V and prothrombin have a direct relationship to the amount of inhibitor administered. These effects could be measured for 24 hours after larger doses. Similar results were obtained in rabbits. In vitro tests using incubated plasma gave parallel but less prompt and less striking results. These authors[95] found no electrophoretic changes in dog plasma after the injection.

They concluded that the lipid inhibitor may have an important role in anticoagulant therapy. Further studies, and especially experience with this substance in man, are essential to determine the validity of this position.

Derivatives of dl-*Alpha-Tocopherol*

Overman and Huebner in our laboratory[96a, b] have been determining vitamin E levels in the blood after the oral and intramuscular administration of several derivatives of *dl*-alpha-tocopherol. It has been possible to increase the level of tocopherol from approximately 1 mg. per 100 cc., which is the normal level, to over 3 mg. per 100 cc. by oral administration of *dl*-alpha-tocopherol acetate. The intramuscular injection of *dl*-alpha-tocopherol phosphate monosodium salt has not increased the free tocopherol level in the plasma. This is probably due to the fact that the phosphate derivative is very stable and probably resists hydrolysis in the body. When Karrer[97] originally prepared *dl*-alpha-tocopherol phosphate in 1940 he indicated that it was very difficult to hydrolyze. The intramuscular injection of *dl*-alpha-tocopherol in sesame oil does not give an increase in plasma level of tocopherol either.

The antithrombin titers of these plasmas at the various levels of *dl*-alpha-tocopherol were also determined by the methods of Quick,[98] Astrup[99] and Kay.[100] The values for the antithrombin times obtained by the method described by Quick are shown in figure 27.

The thrombin solution used contained approximately 20 units per milliliter. This concentration was used because it gave an antithrombin time for the 15 minute incubation period of around 140 seconds. It was thought that any slight changes that might occur in antithrombin titer should be more easily detected at this range. The number of determinations at the various levels of tocopherol are also indicated in the figure. No change in antithrombin titer was detected in the plasmas with a tocopherol level of 0.60 mg. per 100 cc. to 3.2 mg. per 100 cc. at any of the five different incubation periods. The same results were obtained by the use of Astrup's and Kay's methods.

At present we are studying antithrombin titer of two groups of patients who have undergone surgery. One group is being treated according to the method used by Ochsner (tocopherol and calcium) and the other is the control group. Vitamin E, calcium and antithrombin titers are determined daily on both groups. So far we have not detected any change in antithrombin titer in these two groups.

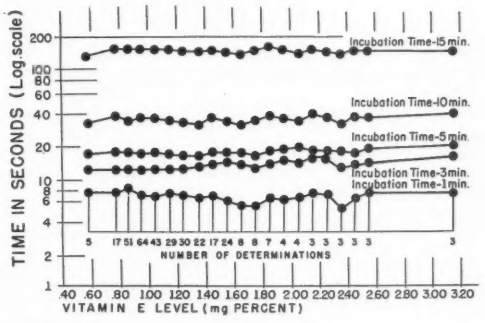


FIG. 27. Average antithrombin times at various vitamin E levels.

A review of the evidence thus far presented and the experience of critical investigators has failed to confirm claims that *dl*-alpha-tocopherol derivatives act as anticoagulant substances when administered to man or have any significant effect in the prevention or treatment of thromboembolic conditions.

The Effect of Certain Antibiotics on the Dosage Requirements of Anticoagulants

Recently we have been impressed by the observation that certain patients who appear well stabilized on a fixed dose of a coumarin derivative may show a marked prolongation of the prothrombin time shortly after starting to receive a gut-sterilizing antibiotic. The incidence of occurrence of this phenomenon appears to have increased with the widespread use of

these antibiotics for all types of cases, especially those of a surgical nature. For example, a patient who requires an average daily dose of 100 mg. of dicumarol (or 600 mg. of Tromexan) to maintain an average whole plasma prothrombin time of 30 to 40 seconds may have a prothrombin time of 60 to 90 seconds within two or three days after starting to take Aureomycin, chloramphenicol or Terramycin. He may require only 25 to 50 per cent of the dicumarol (Tromexan) to maintain times of 30 to 40 seconds. This is at present a preliminary observation only, and should be subject to much closer scrutiny before being finally accepted as conclusive.

The explanation, which must be considered hypothetic at this time, may be found in these facts. The production of vitamin K is largely dependent on the action of the bacterial flora of the intestinal tract. Vitamin K acts as a buffer against the coumarin compounds, holding their action in check to a certain degree. When the bacterial flora are killed off or greatly disturbed, the production of vitamin K is sharply diminished and the action of the anticoagulant drugs is unrestrained, resulting in (a) excessive action and (b) reduced dosage requirements.

Pending confirmation or clarification of these observations, the gut sterilizing antibiotics should be administered with caution when the patient is receiving anticoagulant therapy which interferes with prothrombin production.

Effect of Starvation and a Large Alcoholic Intake on the Anticoagulant Requirements

It has been recognized for some years that undernutrition, especially when the intake of protein foods is involved, appears to render a patient more sensitive to effects of dicumarol. At first we failed to recognize the full significance of this observation, but merely learned to use lower doses to obtain adequate therapeutic levels without danger. During the past decade we have observed this increased response in many malnourished persons. It has not been sufficiently emphasized, however, that many patients are unable to eat satisfactorily following an operation or during an acute or chronic illness. Relatively few days of nausea or vomiting are required to produce such a state. Acute and chronic alcoholism may also lead to a similar condition, with increased sensitivity to dicumarol or Tromexan. These factors must be borne in mind when unusual sensitivity or irregularity of response to these drugs is encountered.

Most of these patients are able to take a quart of milk a day; this supplies important nutrition and frequently stabilizes the utilization of dicumarol as indicated by less fluctuation in the prothrombin time curve.

Summary

The incidence and the serious results of thromboembolic conditions provide some of the most challenging problems in medicine. Until recently little could be done except to observe with respect the devastating effects in the living patient or at the autopsy table. During the past two decades the development of new physical and chemical methods and the advent of the anticoagulant drugs have provided us with tools (a) to study in greater detail the mechanism of thrombosis and (b) to prevent and treat it with greater success than was formerly possible. These technics have been reviewed. In addition, attention has been focused on certain hitherto unemphasized aspects of thrombosis, including the relationship to malignancy, familial and individual thrombosing tendencies, and effects of certain drugs on this process, in the hope of stimulating others to examine them more carefully. Such exploration may result in findings that will help us to understand the general problem.

The new anticoagulants, their actions and dosages, have been briefly reviewed, but no attempt at final evaluation is appropriate at this time.

The problems of increased reaction to coumarin derivatives in the presence of starvation, excessive alcohol and the gut-sterilizing antibiotics have been discussed.

In this modest effort I have tried to give continued expression to the tradition of George E. Brown, whose inquiring mind, ever probing into the outer reaches of knowledge, challenged

many young men to pursue studies in the field of the circulation.

REFERENCES

[1] KNISELY, M. H., BLOCH, E. H., ELIOT, T. S., AND WARNER, L.: Sludged blood. Tr. Am. Therap. Soc. **48–49:** 95, 1950.

[2] —: Blood clotting and other factors. Transactions of the Fourth Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation, 1951. In press.

[3] QUICK, A. J.: On the constitution of prothrombin. Am. J. Physiol. **140:** 212, 1943.

[5] OWREN, P. A.: New investigation on the coagulation of the the blood. Arbok Norske Videnskapsakad. p. 21, 1944.

[4] WARE, A. G., GUEST, M. M., AND SEEGERS, W. H.: A factor in plasma which accelerates the activation of prothrombin. J. Biol. Chem. **169:** 231, 1947.

[5] NOLF, P.: The coagulation of the blood. Medicine **17:** 381, 1938.

[6] FANTL, P., AND NANCE, M. H.: Acceleration of thrombin formation by a plasma component. Nature **158:** 708, 1946.

[7] ALEXANDER, B., DEVRIES, A., AND GOLDSTEIN, R.: A factor in serum which accelerates the conversion of prothrombin to thrombin. Blood **4:** 739, 1949.

[8] JACOX, R. R.: Studies on the activation of a serum "prothrombin converting factor." J. Clin. Investigation **28:** 492, 1949.

[9] QUICK, A. J.: Components of the prothrombin complex. Am. J. Physiol. **151:** 63, 1947.

[10] OWREN, P. A.: A new, previously unknown clotting factor. Scandinav. J. Clin. & Lab. Investigation **1:** 162, 1949.

[11] OVERMAN, R. S.: The chemical purification and mode of action of a thromboplastic inhibitor. Transactions of the Second Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1949.

[12] SEEGERS, W. H.: Activation of purified prothrombin. Proc. Soc. Exper. Biol. & Med. **72:** 677, 1949.

[13] OVERMAN, R. S., AND WRIGHT, I. S.: A new blood clotting inhibitor. J. Biol. Chem. **174:** 759, 1948.

[14] TOCANTINS, L. M., CARROLL, R. T., AND MCBRIDE, T. J.: A lipid anticoagulant from brain tissue. Physiochemical characteristics and action in vitro and in vivo. Proc. Soc. Exper. Biol. & Med. **68:** 110, 1948.

[1] EDSALL, J. T.: Some unsolved problems in the chemistry of the blood. Transactions of the First Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1948. Pp. 49–63.

[16] FERRY, J. D.: Consideration of the structure and mechanism of formation of the fibrin clot. Transactions of the Second Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1949. Pp. 84–105.

[17] HORAN, F. E., HIRSCH, F. G., WOOD, L. A., AND WRIGHT, I. S.: Surface effects on blood-clotting components as determined by zeta-potentials. J. Clin. Investigation **24:** 202, 1950.

[18] WOOD, L. A., HORAN, F. E., SHEPPARD, E., AND WRIGHT, I. S.: Zeta-potential measurements as a tool for studying certain aspects of blood coagulation. Transactions of the Third Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1950.

[19] PAULING, L.: Nature of the Chemical Bond, ed. 2. Ithaca, Cornell University Press, 1948. P. 74.

[20] CHARGAFF, D., ZIFF, M., AND MOORE, D. H.: Studies on the chemistry of blood coagulation. XII. An electrophoretic study of the effect of anticoagulants on human plasma proteins, with remarks on the separation of the heparin complement. J. Biol. Chem. **139:** 383, 1941.

[21] WOLFRAM, M. L., AND RICE, F. A. H.: Electrophoretic resolution of heparin and related polysaccharides. J. Am. Chem. Soc. **69:** 2918, 1947.

[22] LAUFMAN, H., MARTIN, W. B., AND TANTURI, C.: Effect of heparin and dicumarol on sludge formation. Science **108:** 283, 1948.

[23] HAYEM, G.: Sur le mécanisme de l'ârret des hémorrhagies. Compt. rend. Acad. d. sc. **95:** 18, 1882.

[24] BIZZOZERO, J.: Ueber einen neuen Formbestandtheil des Blutes und dessen Wolle bei der Thrombose und der Blutgerinnung. Virchows Arch. f. path. Anat. **90:** 261, 1882.

[25] APITZ, K.: Die Bedeutung des Gerinnung und Thrombose für die Blutstillung. Virchows Arch. f. path. Anat. **308:** 540, 1942.

[26] ZUCKER, M. B.: Platelet agglutination and vasoconstriction as factors in spontaneous hemostasis in normal, thrombocytopenic, heparinized and hypoprothrombinemic rats. Am. J. Physiol. **148:** 275, 1947.

[27] ZUCKER, H. D.: Platelet thrombosis in human hemostasis. A histologic study of skin wounds in normal and purpuric individuals. Blood **4:** 631, 1949.

[28] WRIGHT, H. P.: The role of platelets. Transactions of the Fourth Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1951. In press.

[29] SPOONER, M., AND MEYER, O. O.: The effect of dicumarol (3,3′ methylenebis (4-hydroxycoumarin)) on platelet adhesiveness. Am. J. Physiol. **142:** 279, 1944.

30 Eisen, M. E., Tyson, M. C., Michael, S., and Bauman, F.: Adhesiveness of blood platelets. Circulation **3:** 271, 1951.

31 Moolten, S. E., and Vroman, L.: The adhesiveness of blood platelets in thromboembolism and hemorrhagic disorders. Am. J. Clin. Path. **19:** 841, 1949.

32 Trousseau, A.: Clinique médicale de l'Hotel-Dieu de Paris, Vol. III. Paris, J. B. Bailliere, 1868. P. 95.

33 Nygaard, K. K., and Brown, G. E.: Essential thrombophilia. Report of five cases. Arch. Int. Med. **59:** 82, 1937.

34 Lerner, A. B., and Watson, C. J.: Studies of cryoglobulins. I. Am. J. M. Sc. **214:** 410, 1947.

35 —, Barnum, C. P., and Watson, C. J.: Studies of cryoglobulins. II. Am. J. M. Sc. **214:** 416, 1947.

36 Barr, D. P., Reader, G. C., and Wheeler, C. A.: Cryoglobulinemia. I. Ann. Int. Med. **32:** 6, 1950.

37 McCombs, R. P., and McElroy, J. S.: Reversible autohemagglutinins with peripheral vascular symptoms. Arch. Int. Med. **59:** 107, 1937.

38 Stats, D., and Bullowa, G. M.: Cold hemagglutination with symmetric gangrene of the tips of the extremities. Arch. Int. Med. **72:** 506, 1943.

39 Carey, R. M., Wilson, J. L., and Tamerin, J. A.: Gangrene of the feet and hemolytic anemia associated with cold hemagglutinins in atypical pneumonia. Harlem Hosp. Bull. **1:** 25, 1948.

40 Rønnov-Jessen, V.: Case of primary atypical pneumonia with hemolytic anemia and gangrene of fingers caused presumably by cold agglutination together with survey of subject. Ugesk. laeger **112:** (No. 45) 1548, 1950.

41 Nesser, A. T., and Sachs, I.: Cyanosis due to cold agglutinins. South African M. J. **4:** 953, 1950.

42 Cosgriff, S. W., Diefenbach, A. F., and Vogt, W., Jr.: Hypercoagulability of the blood associated with ACTH and cortisone therapy. Am. J. Med. **9:** 752, 1950.

43 Smith, R. W., Margulis, R. R., Brennan, M. J., and Monto, R. W.: The influence of ACTH and cortisone on certain factors of blood coagulation. Science **112:** 295, 1950.

44 Allen, E. V.: The clinical use of anticoagulants: Report of treatment with dicumarol in 1,686 postoperative cases. J.A.M.A. **134:** 323, 1947.

45 Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases. Philadelphia, W. B. Saunders, 1946. P. 638.

46 Wright, I. S.: Vascular Diseases in Clinical Practice. Chicago, Year Book Publishers, 1948. P. 393.

47 Zilliacus, H.: On the specific treatment of thrombosis and pulmonary embolism with anticoagulants, with particular reference to the postthrombotic sequelae. Acta med. Scandinav. Suppl. **171:** 1, 1946.

48 Crafoord, C., and Jorpes, E.: Heparin as a prophylactic against thrombosis. J.A.M.A. **116:** 2831, 1941.

49 Marple, C., and Wright, I. S.: Thromboembolic Conditions and their Treatment with Anticoagulants. Springfield, Charles C Thomas, 1950. P. 67.

50 Hines, E. A., and Barker, N. W.: Anticoagulant therapy in chronic cardiovascular diseases. M. Clin. North America **33:** 335, 1949.

51 Wise, W. D., Loker, F. F., and Brambel, C. E.: Effectiveness of dicumarol prophylaxis against thromboembolic complications following major surgery. A four year survey, 3504 cases. Surg., Gynec. & Obst. **88:** 486, 1949.

52 Wright, I. S., and Foley, W. T.: Use of anticoagulants in the treatment of heart disease. With special reference to coronary thrombosis, rheumatic heart disease with thromboembolic complications and subacute bacterial endocarditis. Am. J. Med. **3:** 718, 1947.

53 Foley, W. T., and Wright, I. S.: Long term anticoagulant therapy for cardiovascular diseases. Am. J. M. Sc. **217:** 136, 1949.

54 Cosgriff, S. W.: Prophylaxis of recurrent embolism of intracardiac origin. J.A.M.A. **143:** 870, 1950.

55 Askey, J. M., and Cherry, C. B.: Thromboembolism associated with auricular fibrillation. Continuous anticoagulant therapy. J.A.M.A. **144:** 97, 1950.

56 Peters, H. R., Doriges, J. P., and Brambel, C. E.: Further experiences with dicumarol therapy in coronary thrombosis. South. M. J. **41:** 526, 1948.

57 Parker, R. I., and Barker, N. W.: The use of anticoagulants in the management of acute myocardial infarction. Proc. Staff Meet., Mayo Clin. **22:** 185, 1947.

58 Nichol, E. S., and Page, S. W., Jr.: Dicumarol therapy in acute coronary thrombosis. Results in 50 attacks. J. Florida M. A. **32:** 365, 1946.

59 Greisman, H., and Marcus, R. M.: Acute myocardial infarction: Detailed study of dicumarol therapy in 75 consecutive cases. Am. Heart J. **36:** 600, 1948.

60 Freston, J. M., and Taylor, G. M.: Unpublished data.

61 Zeluff, G. W., and Field, W. W.: Anticoagulants in treatment of coronary occlusion with myocardial infarction: A study of eighty cases. New York State J. Med. **50:** 1737, 1950.

62 Smith, F. J., Keyes, J. W., and Denham, R. M.: Myocardial infarction. Am. J. M. Sc. **221:** 508, 1951.

[63] SCHILLING, F. J.: Anticoagulants in myocardial infarction. J.A.M.A. **143:** 785, 1950.

[64] RUSSEK, H. I., ZOHMAN, B. L., WHITE, C. LA V., AND DOEMER, A. A.: Indications for bishydroxycoumarin (dicumarol) in acute myocardial infarction. J.A.M.A. **145:** 390, 1951.

[65] ANDERSON, G. M., AND HULL, E.: The use of dicumarol as an adjunct to the treatment of congestive heart failure. South. M. J. **41:** 365, 1948.

[66] GRIFFITH, G.: Evaluation of anticoagulant therapy in congestive heart failure. Circulation **4:** 416, 1951.

[67] OVERMAN, R. S., STAHMANN, M. A., HUEBNER, C. F., SULLIVAN, W. R., SPERO, L., DOHERTY, D. G., IKAWA, M., GRAF, L., ROSEMAN, S., AND LINK, K. P.: Studies on the hemorrhagic sweet clover disease. XIII. Anticoagulant activity and structure in the 4-hydroxy coumarin group. J. Biol. Chem. **153:** 5, 1944.

[68] VON KAULLA, K. N., AND PULVER, K.: Animal experiments with a new antithrombotic agent, Tromexan. Schweiz. med. Wchnschr. **78:** 806, 1948.

[69] VON REINIS, Z., AND KUBIK, M.: Clinical experiences with a new preparation of the coumarin series. Schweiz. med. Wchnschr. **78:** 785, 1948.

[70] BICKEL, G., AND DELLA SANTA, R.: A new synthetic anticoagulant, the ethyl ester of dicumarinyl acetic acid. Rev. méd. de la Suisse rom. **69:** 546, 1949.

[71] DEUTSCH, E.: Experiences with Tromexan, a new anticoagulant of the dicumarol series. Schweiz. med. Wchnschr. **79:** 1010, 1949.

[72] DE NICOLA, P.: The ethylic ester of di-(4-oxycumarinil) acetic acid and the biological characteristics of its anticoagulant activity. Farm sci. e. tec. (Pavia) **4:** 152, 1949.

[73] ROSICKY, J.: Časop. lék. Česk. **83:** 1200. Quoted by von Kaulla and Pulver.[68]

[74] LIAN, C., SIGUIER, F., WELTI, J. J., PIETTE, M., COBLENTZ, B., AND TRELAT, J.: Reflections on a new anticoagulant. Bull. et mem. Soc. d. hôp. de Paris **66:** 110, 1950.

[75] BURT, C. D., WRIGHT, H. P., AND KUBIK, M.: Clinical tests of a new coumarin substance. Brit. M. J. **2:** 1250, 1949.

[76] OVERMAN, R. S., STAHMANN, M. A., SULLIVAN, W. R., HUEBNER, C. F., CAMPBELL, H. A., AND LINK, K. P.: Studies on the hemorrhagic sweet clover disease. VII. The effect of 3,3′ methylenebis (4-hydroxycoumarin) on the prothrombin time of the plasma of various animals. J. Biol. Chem. **142:** 941, 1942.

[77] OVERMAN, R. S., STAHMANN, M. A., AND LINK, K. P.: Studies on the hemorrhagic sweet clover disease. VIII. The effect of 2-methyl-1,4-naphthoquinone and *l*-ascorbic acid upon the action of 3, 3′ methylenebis (4-hydroxycoumarin) on the prothrombin time of rabbits. J. Biol. Chem. **145:** 155, 1942.

[78] BURKE, G. E., AND WRIGHT, I. S.: A new coumarin anticoagulant (Tromexan) 4,4′ dihydroxy dicumarinyl ethyl acetate: Preliminary report of its action. Bull. New York Acad. Med. **26:** 264, 1950.

[79] HAUSNER, E. P., SHAFER, C. L., CORSON, M., JOHNSON, O., TRUJILLO, T., AND LANGHAM, W.: Clinical evaluation of dicumarinyl derivatives with a metabolic study of the radioactively labeled anticoagulants in animals. Circulation **3:** 171, 1951.

[80] KABAT, H., STOHLMAN, E. F., AND SMITH, M. I.: Hypoprothrombinemia induced by administration of indandione derivatives. J. Pharmacol. & Exper. Therap. **80:** 160, 1944.

[81] SOULIER, J. P., AND GUEGEN, J.: Action hypoprothrombinémiante (anti-K) de la phénylindanedione étudiée expérimentalement chez le lapin. Son application chez l'homme. Compt. rend. Soc. de biol. **141:** 1007, 1947.

[82] JAQUES, L. B.: Personal communication to Blaustein.[78]

[83] BLAUSTEIN, A. U., CROCE, J. J., JR., ALBERIAN, M., AND RICHEY, N.: Preliminary report on the clinical use of a new anticoagulant, phenylindandione. Circulation **1:** 1195, 1950.

[84] IKAWA, M., STAHMANN, M. A., AND LINK, U. P.: The condensation of alpha, beta-unsaturated ketones with 4-hydroxycoumarins. J. Am. Chem. Soc. **66:** 902, 1944.

[85] SCHEEL, L. D., WU, D., AND LINK, K. P.: 4-hydroxycoumarin anticoagulants. Abstract of paper given before the Section of Medicinal Chemistry, Meeting of American Chemical Society, Atlantic City, September 1949.

[86] BATTLE, W. D., CAPPS, R. T., ORTH, O. S., AND MEYER, O. O.: The effects of 4-hydroxycoumarin anticoagulant no. 63 upon the prothrombin time in dogs and human beings. J. Lab. & Clin. Med. **35:** 8, 1950.

[87] MCCARTER, J. C., BINGHAM, J. B., AND MEYER, O. O.: The pathologic findings after the administration of dicumarol. Am. J. Path. **3:** 651, 1944.

[88] HANSON, H., MANN, F., AND BARKER, N. W.: Clinical experience with 4-hydroxycoumarin anticoagulant no. 63, with special reference to the antagonistic effect of menadione and vitamin K_1. Circulation **4:** 844, 1951.

[89] SEIFTER, J., AND BEGANY, A. J.: Studies on the action of a synthetic heparinoid. Am. J. M. Sc. **216:** 234, 1948.

[90] SORENSON, C. W., SEIFTER, J., AND WRIGHT, I. S.: A new synthetic anticoagulant (heparinoid). Preliminary report of its action in humans. Bull. New York Acad. Med. **25:** 448, 1949.

[91] —, AND WRIGHT, I. S.: A synthetic anticoagulant: A polysulfuric acid ester of polyanhydromannuronic acid (paritol): Experience with its use in man. Circulation **2:** 658, 1950.

[92] MARPLE, C. D., AND WRIGHT, I. S.: Thromboembolic Conditions and Their Treatment with Anticoagulants (Monograph). Springfield, Charles C Thomas, 1950.

[93] OVERMAN, R. S.: Discussion of thromboplastin. Transactions of the First Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1948. P. 144.

[94] TOCANTINS, L. M., AND CARROLL, R. T.: Separation and assay of a lipid antithromboplastin from human brain, blood, plasma and plasma fractions. Transactions of the Second Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1949.

[95] COON, R. W., FLYNN, J. E., AND VASSAR, P. S.: In vivo and in vitro effects of a lipid inhibitor of blood clotting. Federation Proc. **10:** 352, 1951.

[96a] OVERMAN, R. S., AND WRIGHT, I. S.: Preliminary report on the absorption of various derivatives of dl-alpha-tocopherol and their effect on antithrombin levels in human plasma. Transactions of the Fourth Conference on Blood Clotting and Allied Problems, Josiah Macy, Jr. Foundation. 1951. In press.

[b] OVERMAN, R. S., AND HUEBNER, R. D.: Personal communications.

[97] KARRER, P., AND BUSSMAN, G.: dl-Alpha-tocopherol-phosphorsaure-ester. Helv. Chim. Acta **23:** 1137, 1940.

[98] QUICK, A. J.: The normal antithrombin of the blood and its relation to heparin. Am. J. Physiol. **123:** 712, 1938.

[99] ASTRUP, T., AND DARLING, S.: Measurement and properties of antithrombin. Acta Physiol. Scand. **4:** 293, 1942.

[100] KAY, J. H., BALLA, G., HUTTON, S. B., AND OCHSNER, A.: The prophylaxis of intravascular clotting by the use of alpha tocopherol and calcium. New Orleans Med. & Surg. J. **103:** 116, 1950.

Acute Atypical Coronary Artery Insufficiency

Incidence and Clinical Course

By DAVID LITTMANN, M. D. AND J. H. BARR, JR., M. D.

Not all patients with acute coronary thrombosis or inadequacy develop classic myocardial infarction. Almost 30 per cent of such patients were found to have atypical and apparently less extensive myocardial injury as estimated by the clinical and electrocardiographic findings. The morbidity as well as the mortality was of a lesser order and a somewhat different therapeutic regimen could be employed.

ACUTE atypical coronary disease is a clinical term applied in this communication to patients with manifestations of coronary insufficiency which are more severe than angina pectoris but which fail to satisfy the criteria for classical myocardial infarction. Included are cases of coronary failure, subendocardial necrosis, and small or obscure myocardial infarctions not demonstrable by present methods.

It is the object of this study to report the incidence of these conditions and to compare their clinical courses, complications and mortality with frank myocardial infarctions.

MATERIAL

The material consists of 207 consecutive patients admitted between July 1946 and June 1950 to the West Roxbury Veterans Administration Hospital* for symptoms arising out of acute coronary inadequacy. Cases were excluded in whom the acute attack occurred more than seven days before admission.

Classification of Material

Typical Myocardial Infarction. In order that it might be clearly separated from other forms of coronary disease, criteria were adopted for the diagnosis of unequivocal myocardial infarction.[1] These included a history of protracted pain unaffected by effort or nitrites, elevations of temperature, elevated white blood count and sedimentation rate, and characteristic electrocardiographic stigmas. Simple T-wave inversion with or without S-T–segment depression was not considered certain evidence of myocardial infarction. Though isolated cases showing such changes may go on to infarction at a later date, the future evolution is ordinarily unpredictable. These cases were not, therefore, designated as myocardial infarction but were otherwise classified.

Since the concepts of coronary failure and of subendocardial necrosis without coronary occlusion are still controversial and possibly obscure, these will be briefly considered.

Coronary Failure. This term was applied by Blumgart and his associates[2–4] to the clinical syndrome of acute coronary disease which is more than angina pectoris but less than infarction. They employed the word *failure* in much the same sense as in the terms *cardiac* failure or *bank* failure, implying inability to fulfill obligations completely or perform necessary functions adequately. This occurs in situations arising from disproportionate and unsatisfied demands upon an inelastic coronary system resulting from increased metabolic requirements, noxious influences or further coronary narrowing, occasionally occlusion. The actual process is considered to be prolonged but *reversible* myocardial ischemia. Myocardial infarction does not occur though this may follow at a later date. There is little or no fever, leukocytosis or accelerated sedimentation. The pain is more lasting and severe than angina pectoris and is unrelieved by rest

From the Veterans Administration Hospital, West Roxbury, Mass.

Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

* Only male veterans are admitted to this hospital.

or nitroglycerin. The blood pressure is maintained and no friction rubs develop. Electrocardiographic changes are said to be either absent, or slight and transient, similar to those seen in angina.

Only two patients of the 207 studied fulfilled these criteria for the diagnosis of coronary failure. There is reason to believe, however, that the limits of this condition, particularly those related to the electrocardiographic changes, may be more flexible than indicated. We have included in this classification patients with T-wave alterations of considerable duration which cleared during the period of hospitalization, ordinarily less than six weeks.

Subendocardial Necrosis (Infarction) without Coronary Occlusion. According to Master and his associates,[5, 6] this condition occurs commonly in individuals with sclerotic coronary vessels and exceptionally when these are normal. Any of a number of stimuli including emotion, hemorrhage, shock, sustained effort, tachycardia, toxic substances or further coronary narrowing leads to a state of myocardial hypoxia. If not promptly relieved this goes on to persistent cardiac pain and eventual necrosis of heart muscle. Destructive changes occur in papillary muscles and in the central myocardium. This localization is related to the character of the coronary vessels and to the ventricular pressure gradient.*[5] These normal phenomena are believed to reduce the blood flow to the deeper layers of the heart which are consequently rendered more liable to injury. The resultant subendocardial injury is diffuse or focal. The endocardial lining is spared, however, and no mural thrombosis occurs. The outer myocardium remains uninvolved and pericardial phenomena do not develop. The small total mass of necrotic muscle causes little or no fever, leukocytosis or increase in red cell sedimentation rate. There is no shock; the blood pressure either remains unchanged or rises while pain is present. The electrocardiographic changes are said to be diagnostic; they consist of S-T–segment depressions with or without T-wave inversions. The former, resulting from injury to the myocardium nearest the endocardium, is the exact opposite of the S-T elevations seen with pericarditis. No QRS changes are seen.

Only those patients were included in this category who demonstrated the characteristic ST-T changes and who had relatively little or no fever or leukocytosis.

Although the terms coronary failure and subendocardial necrosis are intended by their proponents to designate the whole middle ground between angina pectoris and frank infarction, examples of both types are encountered at autopsy. Additionally, as suggested earlier, there may be a third subdivision which cannot be dignified with the diagnosis of classic myocardial infarction. This group, too, demonstrates slight fever, leukocytosis and accelerated sedimentation and shows no evidence of heart failure or peripheral shock. The pain lasts longer than 15 minutes and makes its initial appearance without relation to physical effort. The electrocardiogram tends to run a curious course. Often it is normal on admission, then, slowly over a period of days or weeks, when the patient is asymptomatic, symmetric T-wave inversions occur which persist indefinitely thereafter. Occasionally the record shows T-wave inversions initially which remain without significant change. There are no S-T–segment deviations. These patients are believed to have experienced small and obscurely located myocardial infarctions which are impossible to demonstrate. It might appear that no useful purpose is served by separating these from cases of frank, classic infarction. However, the uncertainty regarding the pathologic process together with the wide divergence of prognosis, clinical course and complications merits this division. For want of a more exact term these cases will be designated atypical myocardial infarction.

* The subendocardial myocardium is considered to have the poorest blood supply because it is nourished by the smallest coronary branches which are farthest from the source and have the least blood pressure. During systole the cavity pressure is identical with or somewhat greater than that in the aorta. This pressure diminishes in the middle layers of the heart and falls to zero at the epicardium. Accordingly, little or no blood flow goes on in the deeper layers of heart muscle during systole. It is restricted in the midzone but is uninhibited at the surface.

Results

The mortality for the entire group of 207 cases was 18.3 per cent. Excluding seven patients who failed to survive the first 24 hours, 15.5 per cent died during the three month period of observation.

Classic Myocardial Infarction. These patients were observed at the same time as the atypical forms and are presented only for purposes of statistical comparison. There were 148 patients in this category. The diagnosis was made when the clinical pattern coincided with the description given earlier. It was not made in the absence of significant Q waves in the electrocardiogram although at times these were difficult to demonstrate.

The mean age was 53 and the range 29 to 80 years. The mortality was 22.4 per cent. It was 19.7 per cent for the 142 patients who survived longer than 24 hours. There were approximately as many posterior as anterior wall infarctions with no significant difference between them in the rate of recovery. First infarctions fared much better than second or third. The mortality in the former was 10.7 per cent, in the latter 51.1 per cent. There were 11 patients in the fourth decade in whom the mortality was 18.1 per cent. In the fifth decade (34 cases) the death rate was 8.8 per cent. Except for this reversal the mortality increased progressively with the age.

The diagnosis of pulmonary infarction was made on 10 patients and suspected in one other. In two this complication was considered to be an important though not the sole cause of death. Both patients had multiple myocardial infarctions and were in congestive failure. Pulmonary infarction was thought to have contributed to death in a questionable but probably minor degree in two other patients. This diagnosis was made in six patients who survived. There were three instances of thrombophlebitis without pulmonary embolization. Except for one group of 25 consecutive patients who formed the basis for another study, most of the patients received prophylactic anticoagulants. In retrospect, however, it appears that in many instances, particularly during 1946 and 1947, inadequate prothrombin suppression was obtained. Despite this, the incidence of thromboembolism was low. In the group of 25 who received no anticoagulants there was one case of thrombophlebitis and none of pulmonary embolism.[7]

Acute, Atypical Coronary Disease

There were 59 patients (28.5 per cent of the total) who failed to satisfy the criteria for classic myocardial infarction. Because of close similarities and overlapping criteria of the component members, considerable difficulty and probable inaccuracies were encountered in their classification. Accordingly, it was felt that the atypical cases could well be considered in a single group as well as separately.

The greatest divergence of the atypical cases from patients with classic infarction was found in the death rate. Only four of the 59 or 6.8 per cent failed to recover. Discounting one patient who was moribund on entry and lived only a few hours, the mortality was 5.1 per cent. One patient who was desperately ill died on the second hospital day. Two other patients died unexpectedly. All of the deaths occurred within 48 hours of admission. Of the surviving 55 cases 11 proceeded to develop frank myocardial infarction following periods of three to 27 days after admission. Although it might be contended that this represented typical infarction from the start,[8, 9] it is considered improbable in view of the development of fresh symptoms in some of these patients and of the completely benign course in all.

Coronary Failure. There were 29 cases in this category. The ages ranged from 27 to 70 years with a mean of 46.4. This was significantly lower than for any other subdivision of acute coronary disease. With one exception, all the patients were less than 60 years of age while one half were under 50. The onset of symptoms occurred during activity in 21 instances, while in eight this took place during rest or sleep. There was a history of previous angina in 15 patients and of myocardial infarction in four. Eleven were experiencing their initial symptoms of acute coronary insufficiency. There were two deaths, a mortality of 6.9 per cent. There were no cases of thromboembolic disease.

With the exception of the two patients who

died, most members of this group were asymptomatic when first seen and remained so thereafter. This was true even when admission took place within two to three hours of the onset. Exceptionally, fleeting anginal twinges were noted during the period of observation. In two patients, however, troublesome angina continued for as long as three weeks. Neither cardiac failure nor peripheral shock occurred in any patient and friction rubs were not heard.

Fever over 99 F. occurred in nine patients; in two it exceeded 100 F. A temperature of 102 F. was seen in one patient who went on to develop classical myocardial infarction and 101.4 F. in another with pneumonitis. The remaining 20 cases were afebrile.

The white cell count varied considerably and appeared unrelated to other signs of illness. Counts were obtained from 5,000 to 17,000 and averaged 9,600. The erythrocyte sedimentation rate was even more variable and totally unpredictable. The electrocardiograms showed striking variations but all became normal in from one day to six weeks.

The two deaths are not easily explained, even in the one patient who was examined post mortem. They must be ascribed to acute arrhythmia or cardiac standstill. Both patients appeared relatively well but died suddenly and without warning. These deaths support the impression that though commonly benign and reversible, this syndrome is potentially hazardous. It may, of course, be purely fortuitous that both patients died at about the same time (within 48 hours of the onset). However, it is likely that such patients are most vulnerable during the first few days of the illness. It is, perhaps, well to assume that coronary occlusion has taken place. The muscle formerly supplied by the now useless vessel may not be infarcted but remains in a delicate, irritable and easily injured state for days or weeks thereafter, or until nutrition has improved through collateral channels. Accordingly, as it did in one patient, actual infarction can occur when the imbalance between coronary supply and cardiac demands is further exaggerated. In other instances this discrepancy may result in disturbances of rhythm which are incompatible with life.

Every effort is directed to keeping the heart at rest and lowering the demands upon it. This should include total bed rest with avoidance of straining or sudden, vigorous movements. Moderate sedation is indicated. The value of oxygen and of prophylactic quinidine is problematic but might, perhaps, be employed on theoretic grounds. There seems to be no place in the treatment of this syndrome for the use of anticoagulants. After 7 to 10 days greater freedom is allowed, but vigorous ambulation is delayed until the electrocardiogram has returned to normal. Use of the electrocardiogram as an index for physical activity is a moot point but appears justified where the patient is asymptomatic, afebrile and has no leukocytosis. Total ambulation is commonly permitted in from two to four weeks, generally in three weeks.

The following case reports illustrate patients of this group.

Case 1. A 38 year old electrician was admitted with a 10 day history of angina pectoris. The pain was first noted while he was engaged in moving his shop to a different location. It promptly subsided with rest and returned inconstantly during effort. On the morning of entry he noted a 20 minute episode of retrosternal squeezing pain which did not result from exertion.

Physical Examination. The patient was well developed and nourished, lying quietly in bed and having no discomfort. The examination was entirely normal. The pulse was 88 and the blood pressure 128/82. There was no fever.

Laboratory Findings. The admission white blood count was 19,000. This was thought to be in error since a repeat determination 24 hours later was found to be 7,400. The sedimentation rate was 5 mm. per hour. The initial electrocardiogram (fig. 1) showed slight but definite S-T– and T-wave changes. On the following day the tracing had cleared and it remained normal thereafter.

Hospital Course. The patient was kept at bed rest and received no medication. He remained afebrile and asymptomatic during the entire hospital course of 24 days.

He returned for a follow-up examination one month later and reported himself free of symptoms. An exercise tolerance test was performed with caution and this was found to be strongly positive.

Case 2. A 48 year old stationary fireman employed at this hospital was admitted with a two

hour history of squeezing substernal pain which had occurred during exertion. During the four months prior to entry he had been troubled with indigestion which seemed to be related to the effort of shoveling coal immediately after lunch. This was always relieved by rest and did not return upon resumption of work. On the day of admission he noted the customary appearance of postprandial epigastric discomfort which differed from previous attacks in that it did not subside with rest.

Physical Examination. The patient, a large, obese, white man was comfortable on admission and the physical examination was entirely negative. The blood pressure was 120/70, the pulse was 88 and there was no fever.

Postmortem Examination. The heart weighed 520 Gm. There were two partial occlusions of the left anterior descending artery, one 2 cm. from the origin and the the other midway down its course along the anterior surface of the heart. The first was made up of gray, friable tissue which appeared recent. The second was yellow, recanalized, old and tough. There was no myocardial infarction by gross or microscopic examination.

Subendocardial Necrosis. This group consisted of 19 patients and was selected almost wholly on the basis of the electrocardiographic findings. It was surprising, therefore, that

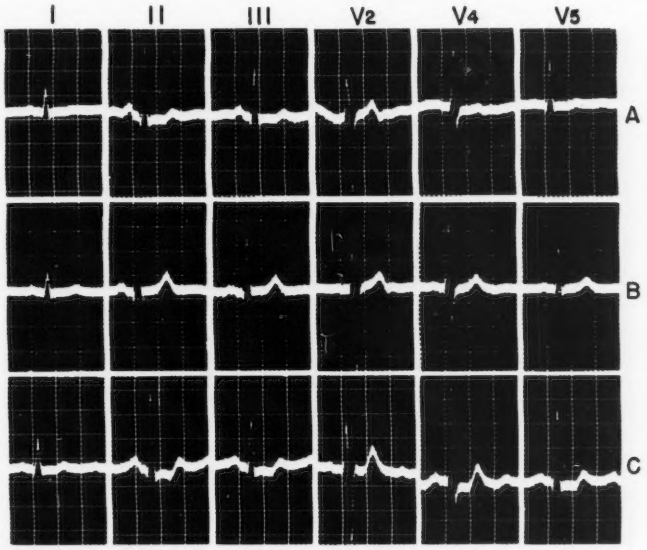


FIG. 1. Case 1. *A.* Electrocardiogram on admission. Note slight S-T segment depressions and low or diphasic T waves. *B.* Normal tracing obtained the following day. *C.* Results of exercise tolerance test; record resembles *A*. This is a positive exercise test.

Laboratory Findings. The only laboratory test performed was a corrected sedimentation rate of 18 mm. per hour. The initial electrocardiogram (fig. 2) showed negative T waves in all the precordial leads. On the following day T_1 became inverted additionally. On the day of death T_1 was diphasic while the precordial leads had become essentially normal.

Hospital Course. Following entry the patient was put to bed and sedated. He also received oxygen and was started on dicumarol. For the first 36 hours he appeared well and had no complaints. During the afternoon of the second hospital day, while in bed, he had a 15 minute episode of mild, squeezing retrosternal pain. At 3:00 a.m. on the morning of the third hospital day, while smoking a cigarette, he gasped once and died.

other details showed such close agreement. The greatest difference from the other classes was in the age which was significantly greater than the rest. The mean was 60 years with a range of 50 to 76 years. Activity of the patient at the onset of symptoms was found to be an unreliable diagnostic detail and could not be used in differential separation. Fewer than half of the group were active when pain first appeared. Severe anemia appeared to be the precipitating factor in three cases. Previous angina pectoris was present in 15 patients. A history of myocardial infarction was obtained in six. The patients appeared much more

seriously ill than those with coronary failure. Significant pulmonary or peripheral edema was apparent in four cases; varying degrees of shock were noted in six. Four patients had both shock and congestive failure and of these two succumbed, both within 48 hours of the onset. These were the only deaths.

Moderate fever and leukocytosis were seen in 12 patients and rather severe angina decubitus was present in three. Despite this, the mortality of 10.5 per cent was well below the rate in the same age group with classic infarction.* No friction rubs were heard and there were no thromboembolic phenomena.†

Six patients of this group proceeded to develop evidence of frank myocardial infarction during the period of hospitalization following intervals of 3 to 27 days. With one exception this took place without recurrence of symptoms and without S-T segment elevation. In these patients it appears likely that coronary thrombosis was present at the outset together with infarction of the deeper myocardial layers. Eventually this extended to involve the entire thickness. That this may actually be so was indicated by one of the two fatal cases that came to autopsy. Although in this instance widespread subendocardial infarction was observed, a fresh thrombosis of the left circumflex artery could also be identified. In three other cases examined post mortem* extensive subendocardial necrosis was unaccompanied by fresh coronary occlusion though widespread sclerosis and old closures could be seen.

Two cases of this group are of special interest. Both were patients with severe pernicious anemia who were admitted for complaints arising out of acute coronary inadequacy. Though seriously ill and showing evidence of

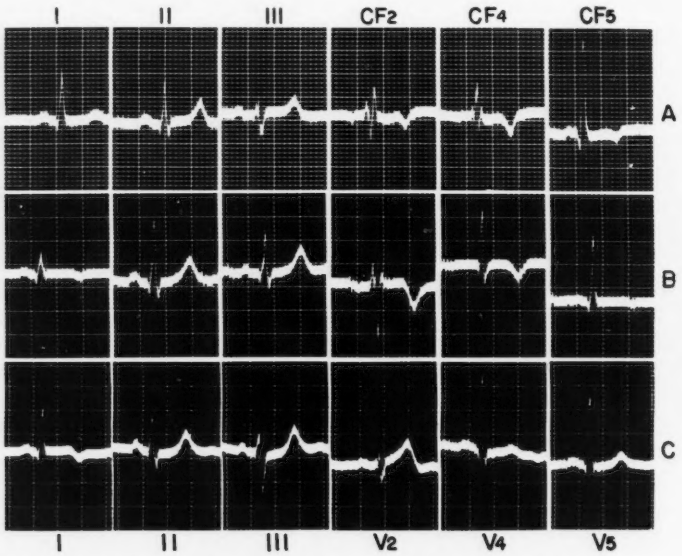


FIG. 2. Case 2. *A*. Tracing obtained on admission. T-wave abnormalities in $CF_{2, 4, 5}$. *B*. Tracing made 18 hours later. Negative T waves in leads I, $CF_{2, 4, 5}$. *C*. Electrocardiogram at 48 hours. (Precordial leads are unipolar and not strictly comparable.) T waves in lead I diphasic and essentially normal in $V_{2, 4, 5}$. The last record was made not long before the patient died.

* 26.9 per cent, our own figures.

† One patient of this type now being studied and not included in this series has had two attacks of subendocardial necrosis. Each lasted six to eight weeks and was accompanied by almost continuous angina decubitus. He has extensive peripheral arteriosclerosis and is considered to have experienced one or more pulmonary emboli in spite of adequate anticoagulant prophylaxis.

* Two recent cases not included in this report.

both congestive failure and peripheral shock, both recovered following blood transfusion, antianemic therapy and cardiac supportive measures.

We have come to associate this condition with rather widespread coronary disease in older people. It is regarded with considerable respect but with a survival expectancy which is better than with frank, transmural myocardial infarction. Spreading infarction may be anticipated in every case but cannot be individually predicted. Where this takes place the subsequent course is relatively benign, possibly because it occurs under ideal circumstances in a heart that has been well conditioned. Both fatalities occurred within the first 48 hours and were anticipated at the outset.

No unusual therapeutic measures were employed in this group except for blood transfusion in the anemic cases. Though thromboembolic phenomena were not seen, anticoagulants were employed largely because of the advanced age of most of these patients and the presence of congestive failure. Wherever possible, ambulation was urged as soon as the temperature and blood counts had remained normal for 7 to 10 days.

Except for some lessening of the S-T segment depression the electrocardiogram frequently retained its abnormal configuration. In five patients, however, the tracing reverted completely to normal.

Only one patient of this group is known to have died after leaving the hospital. This occurred within three months following discharge.

Case 3. A 73 year old Spanish War veteran was brought to the hospital in an almost moribund state. One year earlier he began to experience dyspnea and angina of effort. The pain increased in frequency and duration until it was present most of the time. Dyspnea also increased and edema of the legs appeared. There had been loss of an undetermined amount of weight. The patient was unaware of any pallor.

Examination revealed a well developed, pale, chronically and acutely ill old man. There was evidence of congestive failure with distended neck veins, enlarged liver, pulmonary and peripheral edema. The heart was enlarged. The blood pressure was 100/65, the pulse 110 and the temperature 99 F.

The hemoglobin was 4 Gm., white blood cell count 7,800 and the nonprotein nitrogen 85 mg. per cent. The urine contained albumin, granular casts, numerous white and occasional red blood cells. The electrocardiogram showed widespread S-T depressions and T-wave inversions.

Shortly after admission the patient's condition became critical. The pulse rose to 120 while the blood pressure receded to 70/40. Since it was apparent that anemia was an important factor in the total picture, he was transfused with packed red cells, a total of 4 units in the first 48 hours. He also received digitalis and mercurial diuretics. Despite his desperate state the patient responded well to therapy. Following the fourth transfusion evidence of congestive failure waned, pain disappeared and the blood pressure stabilized. Bone marrow studies were consistent with pernicious anemia. The response to the usual antianemic measures was equivocal, however, and the red blood cell count never rose above 3.6 million cells. The greatest hemoglobin level was 10.7 Gm.

Despite the relative absence of symptoms, the electrocardiogram (fig. 3) first showed extensive improvement then went on to further change. Five days after admission the findings were those of an anteroseptal myocardial infarction.

The patient was released on the forty-sixth hospital day, having been asymptomatic for three weeks. There was no evidence of failure and no angina pectoris. He was still without complaints when seen four months later.

Atypical Myocardial Infarction. There were 11 patients in this category with no mortality. It is, perhaps, the most controversial group, with symptoms and findings most nearly resembling those of mild or small myocardial infarctions.[10] The main point of divergence is the electrocardiogram which simulates the findings of inflammatory heart disease more nearly than those of myocardial infarction. Though it would appear that the injury was anteriorly located in all instances, friction rubs were not encountered except in one patient after he developed a frank transmural infarction. It is suggested that these are instances of small, isolated areas of necrosis which cannot be satisfactorily demonstrated but which, in some instances, enlarge to involve the total thickness of the ventricular wall. As indicated earlier, it is well to separate these patients from the remainder because they carry such a

low incidence of morbidity and, as implied by this series, no mortality.

The average age of 47 years was lower than in classical infarction by 6.3 years. The small number of patients, however, makes the difference questionably significant. The range was 33 to 57 years. There was a history of angina pectoris in four. None had experienced myocardial infarction and seven were having their initial cardiac symptoms. No patient exhibited shock or cardiac failure but 10 of the 11 cases had fever to 99.6 F. The white blood count varied from 7,700 to 19,200 with an average of 12,200. The sedimentation rate was accelerated in every instance.

Two patients in this group had recurrence of symptoms and went on to develop evidence of classical infarction. Electrocardiographic evidence of transmural necrosis occurred in two others who remained asymptomatic. There was no thromboembolic disease despite inadequate prophylaxis in many of these patients. Ambulation was begun early except where extension occurred. Ordinarily such patients were released when the electrocardiogram had stabilized. This occurred in from three to five weeks. In some instances the electrocardiogram remained abnormal and unchanged throughout the period of observation. In two patients gradual and complete return to normal took place within two years.

No one of this group has died or developed evidence of new acute coronary disease in up to four years of observation. One patient has had mild congestive failure during the past two years.

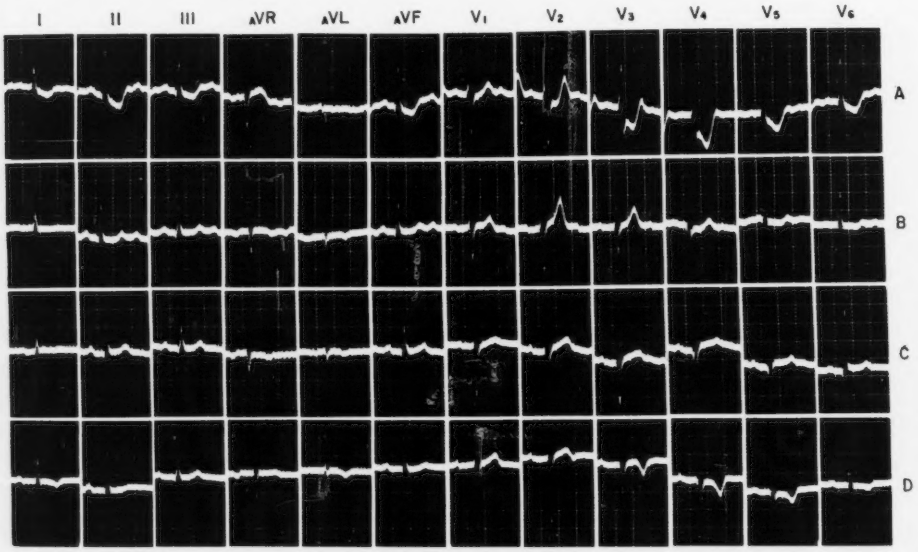


FIG. 3. Case 3. *A*. Electrocardiogram obtained on admission. Findings consistent with severe ischemia and/or subendocardial necrosis. *B*. Second day. Lessened S-T– and T-wave abnormalities. *C*. Fifth day. Fresh changes suggesting early anteroseptal infarction. *D*. Eighteenth day, stable anteroseptal myocardial infarction.

The following cases are considered to be characteristic of the group.

Case 4. A 48 year old letter carrier entered the hospital following a 12 hour episode of intermittent chest pain. While at a movie the day before entry he became dizzy and vomited. A short time later, after a meal, he was seized with a severe, knife-like pain in the left upper chest which persisted until relieved by morphine. On the morning of admission he was awakened by a similar pain which remained until after entry.

Physical Examination. The blood pressure was 105/60, the pulse 70 and the temperature 101 F.

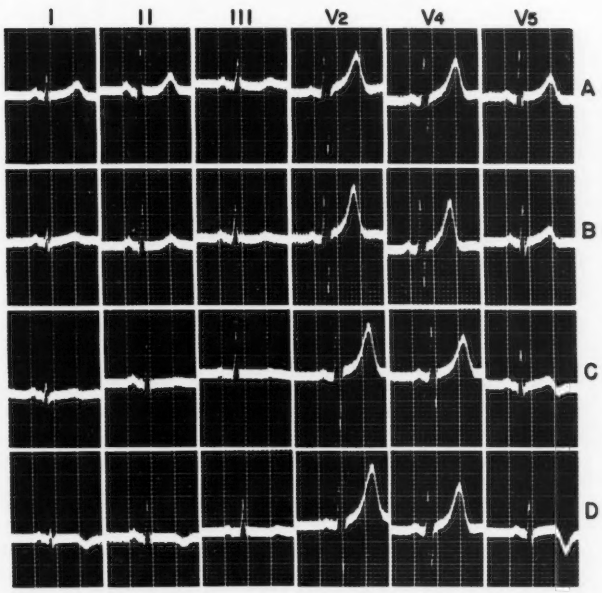


FIG. 4. Case 4. *A*. Normal electrocardiogram on admission. *B*. Fourth day. Electrocardiogram still normal but T waves slightly lower. *C*. Fifth day. Diphasic T in V_5. *D*. Twelfth day. Inverted T in I, II and V_5.

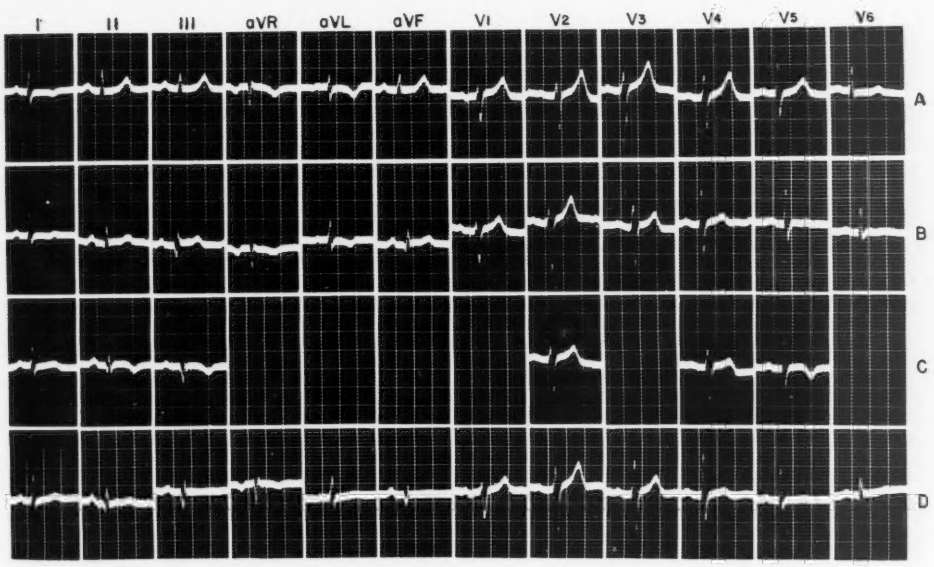


FIG. 5. Case 5. *A*. Electrocardiogram obtained on second hospital day. Negative T in I and aV_L. *B*. Eighth day. T_1 more positive, appearance of Q_2 and Q_3, lowering of $T_{4,5,6}$. *C*. Nineteenth day. Characteristic posterior myocardial infarction with possible anterolateral extension. *D*. Forty-sixth day. Stable posterior infarction.

The patient did not appear ill and the examination was negative except for evidence of sinusitis.

Laboratory Findings. The white count was 12,750 initially and 9,250 on the fifth day. On the sixth day the sedimentation rate was 40 mm. in one hour. Four electrocardiograms (fig. 4) obtained during the first four days were all normal. On the fifth day T-wave changes appeared and one week later T_1, T_2 and T_5 were all symmetrically inverted.

Hospital Course. The patient was placed at bed rest and sedated as required. The temperature fell to normal on the fifth day. While there were no further complaints of chest pain the patient continued to have spells of weakness, faintness, nausea and trembling for the first two weeks. His recovery was otherwise uneventful and he was released on the forty-seventh day. At no time was there any friction rub or other evidence of pericardial reaction.

The patient was seen three months after discharge following a minor constricting anterior chest pain. The electrocardiogram at this time had returned almost to normal and he was not readmitted. When seen sporadically over a period of 18 months he continued to complain of chest pain. An extensive functional overlay made it difficult to determine if he was actually experiencing angina pectoris.

Case 5. A 48 year old transit system foreman was hospitalized with a complaint of retrosternal pain of 48 hours duration. For a number of years there had been symptoms of duodenal ulcer. He had otherwise been entirely well until two days prior to admission when he noted the onset of severe, squeezing chest pain while hurrying for a street car. This subsided after 20 minutes. He was able to work but the pain recurred later the same day and on the morning of admission. On each occasion it was precipitated by effort and lasted for one hour.

Physical Examination. The blood pressure was 120/80, pulse 64 and the temperature was normal. The patient was a moderately obese white male in no distress. The examination was entirely normal.

Laboratory Findings. The white blood count was 8,600 and the sedimentation rate 15 mm. per hour. The initial electrocardiogram (fig. 5) was normal except for a low T_1.

Hospital Course. The patient was placed at bed rest and on an ulcer regimen. He was given nitrites and sedation as needed. During the first week he complained of occasional retrosternal distress which responded to nitroglycerin. On the second hospital day the electrocardiogram exhibited a negative T_1 though the precordial leads were normal. On the seventh day while lying quietly in bed the patient became aware of a retrosternal pain which increased in severity and lasted four hours. It was unrelieved by nitrites. Within 24 hours the white blood count rose to 15,000 and the sedimentation rate to 34 mm. in one hour. Two days later the electrocardiogram showed small Q waves in leads III and aV_F and within 10 days the findings of posterolateral infarction were unmistakable. There was no further pain or fever and the remaining 37 days of the hospital course were uneventful.

The patient was seen three months after discharge. There had been a single transient attack of anginal pain shortly after leaving the hospital; otherwise he had remained free of symptoms.

Discussion

Individual consideration of patients and the treatment of each case according to its own merits are prime ingredients of good medical practice. Such methods, however, have not been widely employed in dealing with "acute coronaries." Although there is general agreement that patients with acute coronary disease vary widely, treatment has become formalized and stereotyped. Except in some desperate situations which may call for unorthodox measures, most patients are treated alike. In recent years there has been a growing tendency to earlier ambulation of patients with myocardial infarction.[11] Such methods, though probably of value in most instances may, however, be detrimental in some. It appears eminently reasonable that a 65 year old patient experiencing his second myocardial infarction (mortality 51 per cent) should be kept in bed longer than a 45 year old patient having his first cardiac injury (mortality 8.8 per cent). Similarly, the almost universal acceptance of anticoagulants has led to the routine use of potentially hazardous drugs in many patients who statistically would not be expected to have thromboembolic phenomena.[12] Such complications are extraordinarily rare in the relatively young patients who are not debilitated, have no obvious peripheral vascular disease, are not in congestive failure and who are encouraged to move around in bed. Yet, just such people are treated with potent anticoagulants and subjected to daily venipuncture together with the attendant discomfort and expense.

Identification and individualization of coronary types should, therefore, serve an exceedingly useful purpose. Those known to carry a low mortality and a trifling incidence of complications, especially the atypical forms, may be spared the discomfort, cost and even dangers of overlong hospitalization and treatment. Con-

versely, where the findings point to more serious disease, longer bed rest and the protection of anticoagulants should be in order. It is of some interest that the degree of cardiac neurosis with which most "coronary" patients leave the hospital is in direct proportion to the length of confinement.

Separation of the atypical forms from the classic and differentiation between them is made largely on the basis of the electrocardiographic interpretation. Currently, the status of this invaluable tool is paradoxic. Clinicians are well aware of the extraordinary accuracy with which this device demonstrates myocardial disease. Despite this, when the electrocardiogram fails to confirm an "obvious clinical impression" it is often dismissed as just another possibly nonspecific laboratory test. As a result, numerous patients with radiculitis or hiatus hernia have been prevailed upon to spend six weeks in bed for "coronary thrombosis or spasm." None denies the positive electrocardiographic findings in myocardial infarction. It is when the tracing fails to confirm that it is discarded. This curious attitude stems from former three- or four-lead days when anteroseptal infarctions were occasionally missed. Such is no longer the case[13] but earlier experiences served to discredit the procedure and this unjustified view has persisted into the present. For such reasons many clinicians are unwilling to make differential separation of the subdivisions of coronary disease by means of the electrocardiogram and be guided in their treatment by this means. Such an attitude is at variance with the statistical results and should be discarded. It is just as unreasonable to regard a case of coronary failure as myocardial infarction as it would be to confound a sprain with a fracture. The surgeon depends on the expertly made roentgenogram for the diagnosis of fracture. The properly made and interpreted electrocardiogram is little, if at all, less specific.

It is suggested, therefore, that when the findings are less than those of frank, classic, transmural myocardial infarction, an attempt should be made to obtain a more accurate and definite diagnosis. The subsequent treatment may then be modified to fit the illness.

Conclusions

1. Analysis was made of 207 consecutive cases of acute coronary artery insufficiency to determine the incidence of atypical forms not characteristically coronary occlusion with myocardial infarction.

2. Fifty-nine cases or 28.5 per cent were separated from the total and considered together as instances of acute atypical coronary artery disease.

3. Further subdivision of this group was accomplished largely on the basis of electrocardiographic differences.

4. There were 29 cases of coronary failure. There were 19 cases of subendocardial necrosis though not necessarily without coronary occlusion. There were 11 cases of atypical (small, obscure) myocardial infarction.

5. The mortality, complications and clinical course of the patients in these subdivisions are tabulated and discussed.

6. Atypical coronary disease is shown to consist of a more benign group of conditions than classic myocardial infarction. Recommendations are made regarding length of hospitalization and therapy.

REFERENCES

[1] Levine, S. A.: Clinical Heart Disease, ed. 3. Philadelphia, Saunders, 1945. P. 108–114.

[2] Freedberg, A. S., Blumgart, H. L., Zoll, P. M., and Schlesinger, M. J.: Coronary failure: the clinical syndrome of cardiac pain intermediate between angina pectoris and myocardial infarction. J. A. M. A. **138:** 107, 1948.

[3] Blumgart, H. L., Schlesinger, M. J., and Davis, D.: Studies on the relation of the clinical manifestations of angina pectoris, coronary thrombosis, and myocardial infarction to the pathologic findings. Am. Heart J. **19:** 1, 1940.

[4] Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Angina pectoris, coronary failure and acute myocardial infarction: the role of coronary occlusions and collateral circulation. J. A. M. A. **116:** 91, 1941.

[5] Masters, A. M., Dack, S., Field, L. E., and Horn, H.: Diagnosis and treatment of acute coronary diseases. J. A. M. A. **141:** 887, 1949.

[6] —: Acute coronary artery disease: history, incidence, differential diagnosis and occupational significance. Am. J. Med. **2:** 501, 1947.

[7] Ohler, R. L.: Personal communication.

[8] Feil, H.: Preliminary pain in coronary thrombosis. Am. J. M. Sc. **193:** 42, 1937.

[9] Sampson, J. J., and Eliaser, J., Jr.: The diagnosis of impending acute coronary artery occlusion. Am. Heart J. **13**: 675, 1937.

[10] Katz, L. N.: Electrocardiography, ed. 2. Philadelphia, Lea and Febiger, 1946. P. 283.

[11] Irvin, C. W., Jr., and Burgess, A. M., Jr.: The abuse of bed rest in the treatment of myocardial infarction. New England J. Med. **243**: 486, 1950.

[12] Dasher, N., and Poindexter, C. A.: Myocardial infarction without anticoagulant therapy: deaths, emboli and an analysis of factors influencing mortality. Am. J. Med. **8**: 623, 1950.

[13] Zinn, W. J., and Cosby, R. S.: Myocardial infarction. II. A re-evaluation of the diagnostic accuracy of the electrocardiogram. Am. J. Med. **8**: 177, 1950.

The Therapeutic Range of Gitalin (Amorphous) Compared with Other Digitalis Preparations

By Robert C. Batterman, M.D., Arthur C. DeGraff, M.D., and O. Alan Rose, M.D.

The therapeutic ranges of amorphous gitalin, digitalis leaf, digitoxin and Digoxin were compared in terms of rapid and slow methods for initial digitalization and maintenance of the digitalized patient. Gitalin (amorphous) possesses a therapeutic range greater than any available digitalis preparation or glycoside. In a group of 18 ambulatory patients, gitalin (amorphous) was found to possess an average of 41 per cent increase in therapeutic range when compared with digitalis leaf. Advantages of the use of gitalin (amorphous) as compared with other digitalis preparations are discussed.

DURING an investigation[1] on the use of amorphous gitalin for the management of the patient with congestive heart failure, it became evident that this medication possessed advantages over other available digitalis preparations and glycosides. It is the purpose of this report to furnish further evidence* that the therapeutic range of amorphous gitalin is greater than that of other digitalis preparations. On the basis of this, it will be demonstrated that amorphous gitalin possesses a greater safety factor when used for either initial digitalization or maintenance.

From the Department of Therapeutics and the Cardiac Clinic, New York University-Bellevue Medical Center; the Adult Cardiac Clinic and Third (New York University) Medical Division, Bellevue Hospital; the Medical Service, Lenox Hill Hospital; and the Cardiac Section of the Medical Service, Bronx Veterans Hospital, New York, N. Y.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors do not necessarily reflect the opinion and policy of the Veterans Administration.

* This investigation was supported by funds allocated by the Committee for the Promotion of Medical Research, Inc., for the study of the treatment of congestive heart failure. Contributors to the Committee for this purpose included White Laboratories, Inc.; Upjohn Co.; Lederle Laboratories, Inc.; Winthrop-Stearns, Inc.; and Campbell Pharmaceutical Co.

The gitalin used in this investigation was supplied under the trade name of Gitaligin by White Laboratories, Inc.

Initial Digitalization—Rapid Method

The use of a digitalis preparation for the treatment of a patient with congestive heart failure is a twofold problem including initial digitalization and maintenance. For initial digitalization, assuming that an oral route is required, the patient is usually given an initial dose and subsequent increments of this dose at intervals of six hours until a therapeutic effect is achieved or toxicity supervenes. The amount of a digitalis preparation required for a satisfactory therapeutic effect cannot be predicted in advance. It must be attained for each individual patient by a trial and error procedure which resembles in many respects a chemical titration for determination of the endpoint. In terms of clinical effect this endpoint is a restoration of myocardial efficiency. As a rule, in the usual patient with congestive heart failure, particularly if this is the first bout of failure, the optimum dose of the digitalis preparation for a satisfactory therapeutic effect can be attained with ease and it is unnecessary to continue further administration of the digitalis preparation at six hour intervals until toxicity occurs. The latter is, of course, undesirable, and may be dangerous. However, with many patients in advanced heart disease, and with patients where the therapeutic effect is not easily discernible, it may be necessary to reach toxicity to assure full digitalization.

When one considers the majority of patients requiring initial digitalization, it is evident that

they possess a good cardiac reserve and that they can achieve digitalization with optimum restoration of myocardial efficiency. It is possible to demonstrate in such patients a therapeutic range for various digitalis preparations. This therapeutic range is obtained by determining the amount of a digitalis preparation required for a therapeutic effect and then cautiously continuing the administration of the digitalis preparation until minor signs or symptoms of toxicity occur. The percentage of the digitalis preparation required for a therapeutic effect in terms of the total dose required for toxicity represents the therapeutic ratio. The smaller the ratio the greater the range. Previous experience with Digoxin[2] and digitoxin[3] indicated that both preparations possess similar ratios (table 1) and that the usual patient required approximately 60 per cent of the toxic dose of the preparations to attain a therapeutic effect. Thus, the therapeutic range under the best circumstances is small. In patients who have marked diminution in cardiac reserve and a small or absent therapeutic range, the use of long-acting glycosides may be dangerous. Overshooting into the toxic level is not uncommon and the toxic manifestations may persist for several days.[3] A review of our patients receiving either U.S.P. XII or XIII digitalis leaf for initial digitalization according to the methods described elsewhere[2–4] revealed that the therapeutic ratio (table 1) is similar to that for Digoxin and digitoxin. In terms of therapeutic range, and indirectly, the safety factor for adequate digitalization with least likelihood of toxicity, digitoxin and Digoxin have no advantage over digitalis leaf. Our experiences with other digitalis preparations including lanatoside C,[5] *Urginea maritima*,[5] *Urginea indica*,[5] and Digilanid[4b] also indicate that these preparations have similar therapeutic ratios. Data[1] on the initial digitalization with amorphous gitalin reveal (table 1) that the therapeutic ratio is significantly smaller than that for digitalis leaf, digitoxin and Digoxin and is indicative of a considerably greater therapeutic range. The usual patient would thus require, in terms of the toxic dose, a smaller dose of amorphous gitalin for a therapeutic effect.

With advanced heart disease, the dose of a digitalis preparation required for a therapeutic effect may approach or equal the dose which will result in toxicity. Because of the very small or absent therapeutic range, digitalization in such a case is usually very difficult. Amorphous gitalin under such circumstances offers an advantage since its greater therapeutic range allows digitalization of some of these patients. However, there are many patients with far advanced heart disease, or with a complication of their heart disease, who manifest toxicity before any therapeutic effect is discernible. Since there has been a complete reversal of the therapeutic range, amorphous gitalin will not compensate for this and it would, therefore, be impossible in this group of patients to achieve satisfactory digitalization regardless of digitalis preparation used. This phenomenon of reversal of therapeutic range cannot be accurately predicted in advance and can only be appreciated after digitalization is attempted. During the process of digitalization, therefore, wherein repeated doses are administered as cautiously as possible to attain a therapeutic effect, it would be expected that

TABLE 1.—*Therapeutic Ratio Determined by Rapid Digitalization (Multiple Dose Method) for Various Digitalis Preparations*

Digitalis Preparation	Number of Patients	Therapeutic Dose		Toxic Dose		Therapeutic Ratio $\left(\frac{\text{Therapeutic Dose}}{\text{Toxic Dose}} \times 100\right)$
		Range	Average	Range	Average	
Gitalin (Amorphous)	24	3.0–10.5 mg.	5.59 mg.	5.25–25.5 mg.	15.11 mg.	36.9
Digitalis Leaf (U.S.P. XII–XIII)	36	0.9– 2.7 Gm.	1.49 Gm.	1.2 – 3.6 Gm.	2.24 Gm.	66.5
Digitoxin	27	0.9– 4.8 mg.	2.39 mg.	1.5 – 9.3 mg.	4.12 mg.	58.0
Digoxin	22	2.0– 6.0 mg.	3.77 mg.	3.0 –12.0 mg.	6.22 mg.	60.6

all of these patients will manifest some type of digitalis toxicity. This toxicity occurs, as a rule, inadvertently, since it results from a dose ordinarily considered to be a safe one and usually below the estimated toxic dose. Nevertheless, its occurrence, although unavoidable, is undesirable. For this reason it is an advantage to utilize a digitalis preparation which possesses a more rapid rate of dissipation than digitoxin or digitalis leaf. This is true of amorphous gitalin. The safety factor for amorphous gitalin used for rapid initial digitalization is therefore twofold. First, digitalization in the usual patient can be attained with a relatively smaller dose of gitalin in terms of the toxic dose than of any other digitalis preparation. Second, toxicity, if it inadvertently occurs with gitalin, will not persist as long as the slowly dissipated preparations.

toxicity is similar to the dosage noted by the more rapid or Eggleston procedure of digitalization. Thus, utilizing digitoxin, it was found[3] that slow digitalization could be achieved in a group of 12 patients with congestive heart failure with an average total dose of 1.7 mg.

A comparable group of patients treated by a multiple dose method required on the average 1.6 mg. The average toxic doses for both groups of patients were also similar. Apparently, as long as the daily dose is sufficiently large the rate of dissipation of the glycoside does not play a role in this phenomenon. Thus, studies[2] with Digoxin, which is more rapidly dissipated than digitoxin, also demonstrated the similarity of dosage for slow and rapid digitalization. When studies[1] along these lines were performed with amorphous gitalin, a difference between this preparation and the other

TABLE 2.—*Comparison of Gitalin (Amorphous) and Digitalis Leaf (U.S.P. XII–XIII) Dosage*

	Gitalin (Amorphous)		Digitalis Leaf	
	Range	Average	Range	Average
Therapeutic Dose	0.25–1.25 mg.	0.45 mg. (0.46 mg. = 0.1 Gm.)	0.05–0.3 Gm.	0.097 Gm.
Toxic Dose	0.75–3.0 mg.	1.19 mg. (0.65 mg. = 0.1 Gm.)	0.1 –0.5 Gm.	0.183 Gm.

INITIAL DIGITALIZATION—SLOW DAILY DOSE METHOD

Initial digitalization can also be attained slowly by administration of a daily dose which is at least two to three times the estimated daily maintenance dose of the patient. If the patient was previously under observation this dose can readily be chosen. However, if the patient is under observation for the first time, one must rely upon accumulated data indicative of predictability of attaining maintenance or toxicity with any daily dose level. Predictability data[6] for digitoxin, Digoxin, lanatoside C and for amorphous gitalin[1] have been previously published. Data[5] for digitalis leaf are similar to data for digitoxin. It is the usual practice for patients who are ambulatory and/or not in severe congestive heart failure to attain slow digitalization by this daily dose schedule. Under this regime the average total dosage to attain satisfactory digitalization and

digitalis preparation was noted. The average total dose for a satisfactory therapeutic effect by both the slow and rapid methods of digitalization was the same, but it was impossible to duplicate the average total dose for toxicity. Several patients continued to take a daily dose, two to three times the predicted maintenance dose, for many days or weeks beyond the anticipated total dose for toxicity. This again reflected the greater therapeutic range for amorphous gitalin. Utilizing this fact, it was possible to digitalize with comparative ease and safety a group of ambulatory patients[1] with mild or moderate signs or symptoms of congestive heart failure.

THERAPEUTIC RANGE—DAILY DOSES—AMBULATORY PATIENTS

Studies on daily dosage required for either maintenance or toxicity also revealed a greater therapeutic range for amorphous gitalin as com-

pared with digitoxin, Digoxin, and lanatoside C. The classic method of determining the percentage of patients who manifest toxicity upon doubling the minimal maintenance dose revealed that the therapeutic ratio for amorphous gitalin was 41 per cent as compared with 64 per cent, 65 per cent, and 63 per cent for Digoxin, digitoxin, and lanatoside C respectively.

Comparison of Amorphous Gitalin with Digitalis Leaf

Although it would appear that for initial digitalization and for maintenance amorphous gitalin possesses a greater therapeutic range than other digitalis preparations, the studies have been performed in different patients. It was, therefore, thought advisable to repeat the studies utilizing the same patient for comparison between amorphous gitalin and digitalis leaf (U.S.P. XII and XIII). Eighteen patients who could be maintained with digitalis leaf were chosen for this phase of the investigation. The minimal daily undivided dose required to achieve adequate maintenance and minimal signs and symptoms of toxicity was determined for both digitalis leaf and amorphous gitalin. Eleven patients presented a greater range with amorphous gitalin than with digitalis leaf. Six patients presented the same range for both preparations, whereas only one patient had a greater range for digitalis leaf. In terms of therapeutic ratio, 12 out of the 18 patients receiving digitalis leaf manifested toxicity upon doubling the minimal maintenance dose, thus giving a ratio of 67 per cent. On the other hand, this occurred in only six of the patients receiving amorphous gitalin, which therefore had a ratio of 33 per cent.

Table 2 presents the range and average dosage for therapeutic effect and toxicity for both amorphous gitalin and digitalis leaf. In terms of average dosage, 0.1 Gm. of digitalis leaf resulted in a therapeutic effect equivalent to 0.46 mg. of amorphous gitalin. The doses for toxicity revealed an average dose of 0.1 Gm. of digitalis leaf equivalent to 0.65 mg. of amorphous gitalin. If the ratio of dosage obtained for the therapeutic effect held for the toxic level then the predicted average amount of digitalis leaf required to produce toxicity should have been 0.257 Gm. Actually the amount was 0.183 Gm. The 41 per cent increase in the average equivalent dosage of amorphous gitalin for the toxic level as compared with the therapeutic dose reflects again the greater therapeutic range of this preparation.

Utilization of Amorphous Gitalin for Patients Not Responding to Digitalis Leaf

Our next consideration was to apply this favorable property of greater therapeutic range of amorphous gitalin for the treatment of patients no longer responding to daily doses of the commonly employed digitalis preparations. It has been our observation that with advanced heart disease, regardless of etiology, the patient may manifest toxicity with a daily dose of a digitalis preparation which previously was adequate for maintenance. Since this dose is no longer capable of producing satisfactory maintenance, it would appear that the therapeutic range for the digitalis preparation is no longer existent. In fact, the range may be reversed, since toxicity occurs with a dose which is insufficient for maintenance. This represents the extreme. There are many patients who present a very small therapeutic range which would require exacting care and skill to achieve satisfactory digitalization and maintenance without toxicity. It is under such circumstances that a digitalis preparation possessing a greater therapeutic range would be of advantage.

This possibility was studied in 20 ambulatory patients who were no longer responding to a digitalis preparation. Every patient required frequent injections of a mercurial diuretic and many, in addition, used daily maintenance doses of an orally administered mercurial diuretic and ammonium chloride. The smallest daily undivided dose of digitalis leaf which would result in minimal signs and symptoms of toxicity was determined in every patient. This was done by increasing at 8 to 10 week intervals the daily dosage of digitalis leaf by increments of 0.05 Gm. until toxicity occurred. The dosage was then decreased to the maximum tolerated dose. All of these patients continued to accumulate edema in spite of this daily maximum

tolerated dose. Since in none of these patients were we able to attain satisfactory maintenance, and toxicity occurred at the next dose level, it was concluded that the therapeutic range for digitalis leaf was either very small and not determinable by the dose schedule used in this investigation or that there was obliteration or reversal of the therapeutic range. Each of these patients was then observed on a daily undivided dose of amorphous gitalin.

Since it was demonstrated that approximately 0.5 mg. of amorphous gitalin was equivalent to 0.1 Gm. of digitalis leaf in terms of therapeutic effect, this dosage schedule was used. The assumption was made that if the therapeutic range was the same for both preparations then the same dosage equivalents should hold for the toxic level. However, if the therapeutic range was greater for amorphous gitalin then the patient should be capable of tolerating an equivalent dosage of amorphous gitalin without toxicity. Thus, 0.5 mg. of amorphous gitalin was substituted for each 0.1 Gm. of digitalis leaf required to produce toxicity. Eleven of the 20 patients manifested toxicity with this dosage schedule. Toxicity occurred within the first four weeks of therapy in eight of these patients, but in three it required from 8 to 16 weeks of continuous daily administration of amorphous gitalin before toxicity occurred. Of greater significance was the fact that 9 of the 20 patients were able to tolerate the equivalent high dose of amorphous gitalin for eight weeks or longer without toxicity. Three of these patients required the next dose level of amorphous gitalin before toxicity occurred, while in one instance a further increase in dosage was still insufficient for toxicity. Improvement in the patient's ambulatory status with a decrease in the severity of the congestive heart failure was noted in 6 of the 20 patients. In one patient improvement was progressive, but at the end of the sixteenth week of therapy toxicity occurred. In another patient, an increase in dosage beyond the estimated toxic dose was required before improvement occurred. Two patients presented a complete control of the decompensation so that it was no longer necessary to administer mercurial diuretics and acidifying salts.

The improvement of six patients and ability of 9 of the 20 patients with advanced heart disease to tolerate dosages of amorphous gitalin which ordinarily should have been toxic are again indications of the greater therapeutic range of amorphous gitalin.

Discussion

The introduction and clinical use of the purified cardiac glycosides have represented an important advance in the treatment of congestive heart failure. The expectancy that the great disadvantage of crude digitalis leaf, that is, the variation from lot to lot, would be obviated by the use of purified glycosides has been fulfilled. It was also hoped that individual glycosides would possess properties unobtainable with the crude galenic digitalis preparations. It was thus possible to utilize the property of a short latent period to attain rapid digitalization with the intravenous administration of ouabain (g. strophanthus), Digoxin and lanatoside C. The oral administration of these preparations, however, did not reflect this desirable property. Similarly, the property of rapid dissipation was of importance since toxic manifestations occurring inadvertently would subside promptly upon cessation of glycoside therapy. This was noted to be true for Digoxin and lanatoside C, but not for digitoxin. These properties of purified glycosides are of importance and allow the physician greater flexibility in the control of his patients with congestive heart failure. However, it has been increasingly evident that even though digitoxin, Digoxin, and lanatoside C, the three purified glycosides in popular use at present, have advantages over crude digitalis leaf, these advantages are not of sufficient magnitude to warrant discontinuation of the use of digitalis leaf. The reasons for this are several. First, the therapeutic range for these three glycosides is similar to that of digitalis leaf. The safety factor for initial digitalization as well as for maintenance is, therefore, the same for digitoxin, Digoxin, and lanatoside C, and digitalis leaf. This should not be confused with the dissipation of toxic manifestation which, because of rapidity for certain glycosides, has been misconstrued to represent greater safety during digitalization. This is true in the sense that

toxicity, no matter how severe, is usually short-lived. However, the possibility of developing severe toxicity is the same for all preparations. Of greater importance is the amount of a digitalis preparation required to restore maximum cardiac efficiency with the least likelihood of producing toxicity. The usual patient requires approximately two-thirds of the toxic dose for digitalis leaf, digitoxin, Digoxin, and lanatoside C to attain a good therapeutic effect. Patients with advanced heart disease and with certain complications of their heart disease may have a narrow therapeutic range. In such a patient the therapeutic dose approaches the toxic dose so that digitalization may be extremely difficult. Overshooting and development of toxic manifestations are not uncommon. The use of digitoxin, Digoxin, and lanatoside C has not corrected this shortcoming of digitalis leaf. If digitalization is difficult with digitalis leaf because of the patient's poor cardiac reserve, the same results will ensue if the aforementioned glycosides are used.

The second disappointment in the use of glycosides is their inability to induce a greater cardiac efficiency than could be achieved with digitalis leaf. As a rule, if the patient no longer responds to digitalis leaf, the substitution of digitoxin, Digoxin, or lanatoside C will not result in a better control of compensation. In our experience, patients with advanced heart disease do not respond to digitalization because they manifest toxicity before the maximum therapeutic effect is evident. In other words, the therapeutic range has been abolished. All digitalis preparations which possess the same therapeutic range will be equally as ineffective for the treatment of the advanced cardiac patient.

Third, the safety of purified glycosides in regard to incidence, type, and severity of toxicity has been misinterpreted. With the exception of local gastrointestinal irritation, and possibly the occurrence of yellow vision, the problems of toxicity associated with digitalis leaf are similar to those of the purified glycosides. Thus, if the patient manifests nausea, vomiting and ventricular premature systoles with coupling following administration of digitalis leaf, the substitution of digitoxin, Digoxin, and lanatoside C in equivalent doses will result in the same type of toxicity. It has been claimed[7] that digitoxin may result in a greater incidence of arrhythmias. There is no doubt that a greater number of arrhythmias have occurred since the use of digitoxin. However, in our opinion it is related to the huge dosage of digitoxin commonly employed rather than the administration of this particular glycoside, per se. In our previous studies[6] with administration of equivalent doses, digitoxin had the same incidence of toxic arrhythmias as Digoxin and lanatoside C. All digitalis preparations in toxic doses may produce very severe and even fatal toxic manifestations. The rapidly dissipating glycosides in this regard have an advantage since toxicity as a rule subsided promptly upon cessation of therapy.

Fourth, it became apparent that "completeness" of absorption of any particular glycoside is not the significant factor for satisfactory clinical usage. The great emphasis placed on the ability of the digitalis preparation to be "completely" absorbed implied that such a glycoside will be more effective than one only partially absorbed. However, digitoxin, the glycoside considered to be one that is "completely" absorbed, will not result in any better or more efficient digitalization than crude digitalis leaf. Of greater importance than the factor of "complete" absorption is the factor of uniformity or constancy of absorption. It is essential that the same amount of the digitalis preparation be absorbed with each dose so that predictability in dosage is a possibility. This is a major problem for the maintenance of the digitalized state since fluctuation in absorption may result in poor maintenance or toxicity. Lanatoside C when administered orally is not very satisfactory because, on the basis of erratic absorption, it is difficult to predict the daily dose in any particular patient. On the other hand, it is relatively easy to do so for digitalis leaf, Digoxin, and digitoxin.

Our studies with amorphous gitalin revealed that many of these criticisms that have arisen with the use of glycosides have been obviated or at least have diminished in importance. On the basis of its greater therapeutic range, it is the safest digitalis preparation available for the treatment of the usual patient with congestive

heart failure. Instead of requiring two-thirds of the toxic dose before attaining a therapeutic effect, the usual patient will respond when approximately one-third of the total toxic dose is administered. This is true for both initial digitalization and maintenance of the digitalized state. Patients not responding to other digitalis preparations because of attainment of toxicity before therapeutic effect may respond to amorphous gitalin. The greater therapeutic range of this preparation permits an easier titration of the patient's cardiac reserve so that a level of dosage may be attained resulting in cardiac efficiency without the occurrence of toxicity. Such patients in the past have been considered refractory to digitalization.

Since the preparation is dissipated at a rate between that noted for digitoxin and Digoxin, amorphous gitalin offers an additional advantage over both these preparations. In some patients, the rapidity of dissipation of Digoxin may result in an inadequate maintenance. On the other hand, the slow dissipation of digitoxin may result in prolonged toxicity if such occurs. Maintenance with amorphous gitalin is very satisfactory. If toxicity occurs, its manifestations will subside more quickly than those noted with digitoxin. This does not exclude the possibility of severe or even fatal toxic manifestations which may occur with all cardiac glycosides. Fortunately, such occurrences are uncommon. It is, however, a definite advantage to have a preparation whose rate of dissipation would make prolonged toxicity unlikely.

Finally, amorphous gitalin possesses uniformity in potency and absorption. Variation from lot to lot was not observed in the clinical use of four different batches of amorphous gitalin. Uniformity in absorption assures satisfactory digitalization and maintenance with predictable doses.

Summary and Conclusions

1. Gitalin (amorphous) possesses a therapeutic range greater than any available digitalis preparation or glycoside.

2. Initial digitalization by either rapid or slow methods and maintenance of the digitalized state can be attained with gitalin (amorphous) with a greater degree of safety than heretofore.

3. The usual patient requires, in terms of the toxic dose, a much smaller dose (approximately one-third) of amorphous gitalin for a therapeutic effect.

4. When compared with digitalis leaf by determining the minimal therapeutic and toxic doses in the same patient, gitalin (amorphous) was found to possess an average of 41 per cent increase in therapeutic range.

5. Patients refractory to digitalis because of inability to attain improvement in cardiac efficiency without the occurrence of toxicity, may do so with amorphous gitalin on the basis of its greater therapeutic range.

6. On the basis of therapeutic range, dissipation, uniformity from lot to lot, constancy in absorption, gitalin (amorphous) is the digitalis preparation of choice for the treatment of the usual patient with congestive heart failure.

References

[1] Batterman, R. C., DeGraff, A. C., Gutner, L. B., Rose, O. A., and Lhowe, J.: Studies with gitalin (amorphous) for the treatment of patients with congestive heart failure. Am. Heart J. **42**: 292, 151.

[2] Rose, O. A., Batterman, R. C., and DeGraff, A. C.: Clinical studies on digoxin, a purified digitalis glycoside. Am. Heart J. **24:** 435, 1942.

[3] DeGraff, A. C., Batterman, R. C., and Rose, O. A.: Digitoxin, its evaluation for initial digitalization of the patient with congestive heart failure. J. A. M. A. **138:** 475, 1948.

[4a] Batterman, R. C., Rose, O. A., and DeGraff, A. C.: The combined use of ouabain and digitalis in the treatment of congestive heart failure. Am. Heart J. **20:** 443, 1940.

[b] —, Holman, D. V., and DeGraff, A. C.: The therapeutic effectiveness and potency of digilanid in the treatment of congestive heart failure. Ann. Int. Med. **14:** 2058, 1941.

[5] Unpublished data.

[6] Batterman, R. C., and DeGraff, A. C.: Comparative study on the use of the purified digitalis glycosides, Digoxin, digitoxin, and lanatoside C, for the management of ambulatory patients with congestive heart failure. Am. Heart J. **34:** 663, 1947

[7] Levine, H. D.: Abnormal rapid rhythms associated with digitoxin therapy. Ann. Int. Med. **29:** 822, 1948.

An Evaluation of Replacement Fluids in Laboratory Animals following Control Hemorrhage

By A. Ervine Morrison, Jr., M.D., John S. Lundy, M.D., and Hiram E. Essex, Ph.D.

Solutions of Dextran Ph, Plasmoid, Periston and isotonic saline were compared with serum albumin and whole blood to determine the efficacy of the former as blood substitutes. Rats, guinea pigs and dogs were used as experimental animals. Dextran Ph, Plasmoid and Periston were found to be less satisfactory than whole blood, since 50 to 80 per cent of the rats and guinea pigs survived following their use compared with 100 per cent survival when whole blood was given. There was, however, 100 per cent mortality of the animals when a blood substitute was not given.

IN TIME of war or national emergency, there has usually been urgent need for materials which can be produced in quantity for treatment of shock resulting from trauma or acute loss of blood or plasma, because the supply of blood and plasma may not be adequate or readily available.

It is also recognized that it would be wise to have at hand proper substances for transfusion of patients in small hospitals and in rural areas where blood transfusion service is not adequate. For use in such places the primary considerations for a plasma substitute are availability, stability, relative inexpensiveness, and ease of administration.

The substances which are the subject of this investigation may be produced in large quantities and stored in depots for emergency use with less danger of deterioration or contamination than would be true of blood or plasma. Since these substances have been used clinically and have been found to have a favorable effect in combatting hypotension, it was deemed advisable to compare them in laboratory animals in order to determine whether any one of these substances was significantly superior to the others.

From the Mayo Foundation, University of Minnesota, and the Mayo Clinic, Rochester, Minn.

Abridgment of thesis submitted by Dr. Morrison to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Anesthesiology.

Materials and Methods

In this study, Dextran Ph (a polysaccharide of high molecular weight), Plasmoid (osseous bovine gelatin) and Periston (a synthetic polyvinyl pyrollidine) were compared with isotonic saline solution, human serum albumin, human plasma, and blood in various species of laboratory animals following control or graded hemorrhage.

The Dextran was furnished by the Pharmacia Company, of Stockholm, Sweden, and was manufactured and bottled by them. The Dextran Ph was a 6 per cent solution of Dextran in a 0.9 per cent sodium chloride solution.

The gelatin solution, Plasmoid, used was a 5 per cent bovine osseous gelatin in an isotonic solution of sodium chloride. It was furnished by the Upjohn Company. This solution was prepared from the collagen of the long bones of cows by electrodialysis and treatment with steam under pressure.

The Periston was furnished through the Interchemical Corporation by I. G. Farben, of Germany, in a 20 per cent concentration in 50 cc. ampules. This was diluted with Ringer's solution and a 3.5 per cent preparation was made according to the recommendation of Weese, the discoverer. Prior to our investigation with blood replacement, antigenic studies were carried out in guinea pigs and rabbits with this material. Additional tests for pyrogens, toxicity and sterility of the Periston were done by the Interchemical Corporation with negative results.

In evaluating these substances in the laboratory, it was decided that more than one species of animal should be used. Therefore, albino rats, guinea pigs and dogs were used. The effects of these substances under investigation were compared with those of isotonic saline solution and heparinized blood. Observations on the value of human serum albumin and human plasma were also made in some experiments.

Different investigators have used various methods to compare the effectiveness of blood and plasma substitutes. Some[1–3] have used animals that have had tourniquets applied to their thighs for protracted periods; others have used manipulation of exposed intestines,[4–6] burns,[7] trauma of thighs[8] and various types of graded hemorrhage.[9–19]

Since Dextran Ph, Plasmoid and Periston have been used as blood substitutes, they were chosen for this study to replace the blood volume lost by hemorrhage. Guinea pigs were studied first. Several exploratory methods were used to find that method by which blood could be removed most effectively and a replacement agent could be most readily given. Direct cardiac puncture and cannulation of the femoral vein were tried but were found unsatisfactory. For the observations on guinea pigs the right jugular vein was cannulated with the animal under drop ether anesthesia. The right jugular vein was exposed and through a small incision a small caliber polyvinyl plastic tubing was passed down the jugular vein to the region of the right atrium. The tubing was held in position by ligatures, and the distal portion of the vein was tied off. The plastic tubing was attached to a syringe by which blood could be removed rapidly and one of the replacement fluids could be injected with ease. After this procedure, the plastic tubing was removed, and the jugular vein was ligated proximally. The guinea pig was then allowed to recover from the anesthetic. Using this method for bleeding and infusing these fluids, we found a bleeding volume which would be 100 per cent lethal to the guinea pig.

Albino rats were also observed with use of similar methods. The left carotid artery was exposed, and a small plastic tubing was inserted for a few millimeters and held in place with a ligature. A syringe was attached to the plastic tubing, and blood was removed and one of the infusing agents injected through the carotid artery.

In the technics used for guinea pigs and rats, it was found necessary to accomplish the foregoing procedure of hemorrhage and infusion in 10 minutes or less. If a longer period was required, recovery was unlikely to occur. Signs of air hunger were very pronounced after the hemorrhage.

Only those guinea pigs and rats which recovered from the anesthetic and the immediate procedure and assumed an upright position after an infusion were included in the results of these experiments. If these animals survived 24 hours or longer, they were considered survivals.

The evaluation of the replacement fluids was recorded in graphic form. The number of survivals of the 10 experimental animals used for each substance is shown (figs. 1 and 2).

In the study of these replacement agents in dogs, it was found necessary to use other methods than were used with the guinea pigs and rats. Ivy and associates[17] reported a great variation in survival of dogs undergoing hemorrhages of various degrees. It became quite evident after the initial trials that not all dogs could tolerate the same relative amount of hemorrhage. The method described by Lawson[18] seemed quite adequate for evaluating the replacement fluids and was adopted.

The method of Lawson[18] was modified to the extent that local anesthesia and inhalation of ether were substituted for barbital anesthesia. The dogs

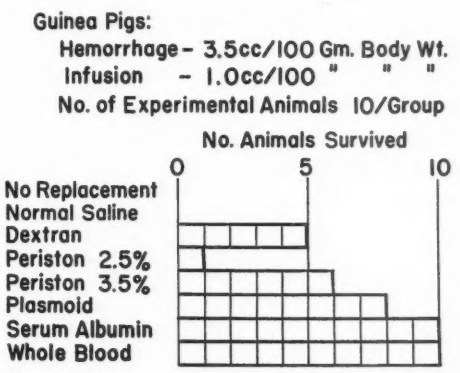


FIG. 1. Survival of guinea pigs undergoing experimental hemorrhage and infusion of various replacement fluids.

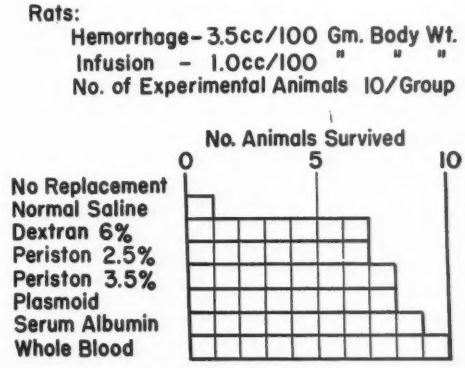


FIG. 2. Survival of rats undergoing experimental hemorrhage and infusion of various replacement fluids.

were unselected mongrels of both sexes and weighed from 6.5 Kg. to 27.2 Kg. Food and water were withheld for a period of 15 to 18 hours preceding the experiment. Then a hemorrhage of 20 cc. per kilogram body weight was accomplished at the rate of 2 cc. per kilogram per minute. With the animal under 1 per cent procaine hydrochloride infiltration anesthesia, the right jugular vein was exposed and a small polyvinyl tubing was inserted into its lumen and held in place with ligatures. The vein was tied

off distally. The tubing was inserted to a point near the right atrium. Occasionally the tubing passed directly into the right atrium or ventricle. The desired quantities of blood were removed by aspiration with a syringe. The vein was then ligated and could be used again later.

Two hours after this first hemorrhage, the animal was anesthetized in a closed ether chamber. An intratracheal tube was passed into the trachea and attached to an ether can which had inspiratory and expiratory valves in the circuit, so that the animal breathed ether through a one-way system. The carotid artery was exposed, a glass cannula was inserted, and continuous blood pressure readings were recorded by means of a mercury manometer and kymograph. A polyvinyl plastic tubing was again passed down the right jugular vein to the region of the right atrium, and blood was removed by aspiration with syringes. A measured amount of blood, 2 cc. per kilogram, was then removed every three minutes until the blood pressure was less than 60 mm. of mercury. This amount of blood removed was designated as H_{1a}. The end point used for this bleeding volume was a blood pressure of 50 to 55 mm. of mercury. Shortly after this point had been reached, one of the substances to be tested was infused through the same jugular vein in a quantity equal to the amount of blood removed. This quantity of replacement fluid was designated as R.

The carotid artery and the jugular vein were tied off, and the animal was allowed to recover. Four hours later the animal again underwent hemorrhage under local anesthesia at the rate of 2 cc. per kilogram per 3 minutes until it died. This last bleeding volume was designated as H_2. The residual blood volume after H_{1a} had been removed was estimated, using Lawson's figure of 10.10 cc. per kilogram, and was designated as H_{1e}. H_{1a} and H_{1e} were then added together and called H_1. The ratio of H_2 to H_1 was then compared and multiplied by 100, and a percentage value was obtained.

An additional observation was made on 15 dogs during the procedure just described. Electrocardiograms were taken on three dogs of each series. Control electrocardiograms were taken before and after etherization. Electrocardiograms were again taken after the H_{1a} hemorrhage, after the infusion of one of the replacement agents, again before H_2, and during the H_2 hemorrhage.

In all of the experiments the hemorrhage was done with the animals in a supine position.

Since many of the blood substitutes which have been used in the past have been found to have noxious or deleterious effects, including accumulation in certain organs of the body, the substances under investigation were administered at intervals to a series of guinea pigs over a prolonged period. Twenty male guinea pigs were used for this purpose. The weights of the animals were recorded at the beginning of the experiment and again at its termination. The materials were given into the penile vein. Occasionally it was impossible to make an intravenous injection and the replacement fluid was then given intraperitoneally. Twenty injections were given to 12 guinea pigs over a period of two months. Because of the death of three guinea pigs following injections of contaminated Plasmoid, three additional guinea pigs were substituted and received nine injections intravenously over a period of three weeks. Five guinea pigs were used as control animals.

It was found that contamination of Plasmoid solution with bacterial growth was more prone to occur than contamination of Periston or Dextran after the bottle was opened. Periston and Dextran appeared to be highly resistant to bacterial contamination.

Results

Six guinea pigs and three rabbits were used as experimental animals for antigenic tests with Periston. The guinea pigs were divided into two groups. Two solutions were prepared. One solution contained 10 per cent Periston (polyvinyl pyrollidine) in distilled water; and the second solution contained 10 per cent Periston mixed with egg albumin (20 cc. in 80 cc. distilled water), equal amounts of each. Three guinea pigs were injected with the 10 per cent solution of Periston, being given 1 cc. each; and three guinea pigs were injected with 1 cc. each of the Periston and egg albumin solution, the solutions being given intravenously. Twenty-one days later, all six guinea pigs were given intravenously 1 cc. of 10 per cent solution of Periston. No noticeable effects were seen in any of the guinea pigs. One of the guinea pigs which had received only Periston previously was given 1 cc. of the Periston and albumin mixture without effect. The three guinea pigs which had been given the mixture of Periston and egg albumin were given 1 cc. of this mixture. In these three guinea pigs an anaphylactic reaction promptly developed and the animals died. From this experiment it appears that Periston is not antigenic.

Three rabbits were used to determine further the possible antigenic properties of Periston. The effects of intravenously infused Periston on blood flow was observed in one rabbit by means of a transparent chamber inserted in one ear. Each of the three rabbits was given 5 cc. of 4 per cent solution of Periston intravenously.

The infused Periston appeared to have no effect on the general condition of the rabbits. The blood flow through the vessels in the transparent chamber was observed for a period of 45 minutes. There was no leukotactic phenomenon exhibited as has been reported by Essex and Graña[20] following the intravenous administration of solutions of Dextran, acacia and other materials.

Three weeks later, 10 cc. of 4 per cent solution of Periston in distilled water was given intravenously to the same three rabbits. There resulted no anaphylactic reactions or other signs of allergy. The circulation of the blood through the rabbit's ear was again visualized after the administration of Periston, and again there was no leukotactic response. If anything occurred, it was an increase in the rate of the circulation of the blood.

Bleeding volumes were completed in a series of 15 guinea pigs by removal of blood from the region of the right auricle through small plastic tubing. The average amount of blood that could be removed was found to be 3.85 cc. of blood per 100 Gm. of their body weight. All the guinea pigs died after the removal of this quantity of blood. After this, guinea pigs were bled 3.0 cc. per 100 Gm. and 3.5 cc. per 100 Gm. of their body weights. If the blood lost by these hemorrhages was not replaced the guinea pigs died.

With a hemorrhage of 3 cc. per 100 Gm. body weight followed by an infusion of one of the replacement fluids in the quantity of 1 cc. per 100 Gm. of body weight, there appeared to be relatively little difference in the rate of survival, with the exception of the controls that received saline solution. If the blood lost was not replaced or if infusions of isotonic saline solution were given, there were no survivals. The survival rate following the infusion of Dextran 6 per cent, Periston 3.5 per cent, Plasmoid and serum albumin was 100 per cent. The survival rate following the infusion of heparinized guinea pig blood strangely enough was 90 per cent. Ten guinea pigs were used for each comparison.

In another series of guinea pigs from which 3.5 cc. of blood per 100 Gm. was removed, survival rates without replacement and after the infusion of 1 cc. isotonic saline solution per 100 Gm. were the same as the survival rates of those from which 3.0 cc. of blood per 100 Gm. was removed in that there were no survivals. After infusion of Dextran Ph the survival rate was 50 per cent; after infusion of 3.5 per cent solution of Periston the survival rate was 60 per cent; after infusion of Plasmoid the survival rate was 80 per cent; after infusion of human serum albumin or of heparinized guinea pig blood the survival rate was 100 per cent (fig. 1).

A similar type of hemorrhage was carried out on albino rats. The rates of survival following a hemorrhage of 3.5 cc. per 100 Gm. body weight with no replacement or replacement of 1 cc. of the materials per 100 Gm. were: (1) no replacement, 0 per cent; (2) isotonic saline solution, 10 per cent; (3) Dextran Ph, 70 per cent; (4) Periston, 3.5 per cent, 80 per cent; (5) Plasmoid, 80 per cent; (6) human serum albumin, 90 per cent, and (7) heparinized rat whole blood, 100 per cent (fig. 2).

TABLE 1.—*Results in Evaluation of Various Replacement Agents in 43 Dogs**

Replacement fluid	Animals	Mean	Standard deviation
Blood	5	94.6 ± 3.6†	8.1
Plasma	2	78.4 ± 0.5	0.7
Dextran	10	77.1 ± 3.3	10.5
Plasmoid	9	68.1 ± 3.8	11.5
Periston 3.5%	10	68.1 ± 4.3	13.6
Saline solution	7	51.1 ± 7.3	19.3

* Mean percentage ratios: $\frac{H_2}{H_1} \times 100$

† The value following the ± is the standard error of the mean.

Using the Lawson technic for the comparison of blood and plasma substitutes, with the modification already described, the results of the evaluation of these replacement fluids in the dogs (presented as mean percentage ratios) are as shown in table 1.

In the series of 20 guinea pigs used for infusion of these replacement fluids, before necropsy, the animals were again weighed. Determinations of hemoglobin and complete blood counts, including erythrocytes, leukocytes, lym-

phocytes, heterophils, eosinophils and immature cells, were performed. The results of these blood counts are seen in table 2. The guinea pigs were killed in a chloroform chamber and necropsies were done immediately. There were no gross changes to be seen in any of the animals. Tissue specimens of the heart, lungs, aorta, liver, spleen, kidneys and bone marrow

TABLE 2.—*Results of Complete Blood Counts in Control and Experimental Guinea Pigs after Prolonged Administration of Replacement Agents.*

Hemoglobin, Gm. per 100 cc.	Erythrocytes, millions per cu. mm.	Leukocytes, thousands per cu. mm.	Lymphocytes, per cent	Heterophils, per cent	Eosinophils, per cent
Control series: no infusion					
12.8	4.7	7.6	39	61	0
13.0	4.7	7.6	44	53	0
14.8	5.8	9.2	53	43	3
12.4	3.45	12.8	36	64	0
13.0	4.95	4.8	54	44	0
Dextran Ph infusions					
12.4	4.25	12.2	80	19	1
13.2	4.05	4.8	74	26	0
13.6	4.15	8.1	76	24	0
13.9	3.95	4.8	62	38	0
11.6	3.50	12.5	80	15	0
Periston 3.5 % infusions					
11.2	3 70	11.5	71	27	4
13.0	3.40	6.0	76	24	0
12.0	3.55	10.7	48	49	0
13.6	3.35	8.5	66	34	0
14.6	4.35	—	75	25	0
Plasmoid infusions					
12.8	3.45	8.5	66	34	3
13.2	4.65	14.4	61	39	4
—	3.90	10.5	56	42	1
10.8	3.30	6.2	85	15	0
12.6	—	—	—	—	—

smears were saved for further examination and comparison with the control specimens.

On microscopic examination of the tissues of the guinea pigs, there were no variations from the normal control tissues observed, in those guinea pigs which had received Dextran Ph and Plasmoid. In the guinea pigs receiving Periston, there were observed bluish vacuolated cells in the liver and spleen. This bluish staining material appeared to have been absorbed by the Kupffer cells and other macrophages in the liver and spleen. The significance of this variation was undetermined.

COMMENT

The problem of replacing blood lost by hemorrhage is of major importance to the surgeon and the anesthesiologist as well as to other medical practitioners. This is particularly so in the prophylaxis and treatment of operative shock. No one disputes the efficacy of whole blood in these regards. However, we were concerned with evaluating replacement fluids other than blood and blood derivatives. At times blood and blood derivatives may not be readily available. The substances evaluated in this study are readily stored and are relatively inexpensive.

The results of these experiments reveal a definite superiority of the replacement fluids evaluated when compared with isotonic saline solution. In dogs, there was no significant difference between human plasma and Dextran Ph. There appeared to be a superiority of Dextran Ph over Plasmoid and Periston, but it was not statistically significant.

In the guinea pigs treated with human serum albumin, a survival rate of 100 per cent was comparable to that of guinea pigs that had received blood. Plasmoid appeared superior to Dextran Ph and Periston 3.5 per cent.

In the albino rats, serum albumin was found to be superior to Dextran Ph and Periston 2.5 per cent as a blood substitute. Dextran Ph, Periston 2.5 per cent, Periston 3.5 per cent and Plasmoid were about of equal value.

The value of survival rates as a method of evaluating replacement fluids in small animals after hemorrhage may be questioned. The effects of cerebral anoxia and cardiac damage on survival must be borne in mind.

A comparison of the mean percentage ratios obtained in our experiments on dogs with the results obtained by Lawson indicated that our values were consistently higher than his. A possible explanation for this fact may lie in the nature of the anesthetic agents used. In our experiments, ether was used, which causes the

spleen to constrict, and thus the circulating volume of blood is augmented. A barbituric acid derivative was used by Lawson. Dilatation and engorgement of the spleen are known to follow administration of these agents. Further it has been shown by Pender and Essex[21] that, under the conditions of their experiments on traumatic shock in dogs, those anesthetized with barbiturates lived longer than those anesthetized with ether.

In the efforts to determine whether deleterious effects or pathologic changes followed prolonged intravenous administration to animals of the replacement fluids, nothing of significance was observed, but two findings of interest might be mentioned here. Their significance, however, is undetermined.

There occurred a reversal of the differential count of the lymphocytes and heterophils (table 2). In all but one of the guinea pigs which had received the Dextran Ph, Plasmoid or Periston, the lymphocyte count was greater than the heterophil count. Three of the five animals in the control series showed a higher heterophil count than lymphocyte count.

The second finding of interest was the electrocardiograms taken on the 15 dogs and the response of the animals to the infusion of the replacement fluids. The recovery rate of the electrocardiogram after the original hemorrhage and the subsequent rhythm changes and alterations in the complexes, particularly the T waves, were noted. In this series there was an apparent correlation between the mean percentage ratios and the electrocardiographic changes. The electrocardiographic changes or the lack of them provided a strikingly reliable indication of the probable survival time of these animals and the necessity of a replacement fluid.

Summary

An evaluation has been made of the efficacy of certain fluids when used for replacing blood lost by hemorrhage in guinea pigs, albino rats and mongrel dogs.

Hemorrhages of 3.5 cc. per 100 Gm. of body weight were found to produce death in all guinea pigs and rats if one of the plasma substitutes was not used.

The survival rates in guinea pigs after a hemorrhage of 3.5 cc. per 100 Gm. were as follows: without plasma substitute, 0 per cent; with replacement with 1 cc. of the following liquids per 100 Gm. of body weight: isotonic saline solution, 0 per cent; Dextran, 50 per cent; 3.5 per cent solution of Periston, 60 per cent; Plasmoid, 80 per cent; serum albumin or heparinized guinea pig blood, 100 per cent.

The survival rates in albino rats after a hemorrhage of 3.5 cc. per 100 Gm. were as follows: without plasma substitute, 0 per cent; with 1 cc. of the following liquids per 100 Gm. of body weight: isotonic saline solution, 10 per cent; Dextran, 70 per cent; 3.5 per cent solution of Periston, 80 per cent; Plasmoid, 80 per cent; serum albumin, 90 per cent; heparinized rat blood, 100 per cent.

Using the Lawson method for the evaluation of replacement fluids, we obtained the following mean percentage ratios $[(H_2/H_1) \times 100]$: heparinized dog blood 94.6 $\pm$ 3.6, human plasma 78.4 $\pm$ 0.5, Dextran 77.1 $\pm$ 3.3, Plasmoid 68.1 $\pm$ 3.8, Periston 68.1 $\pm$ 4.3, saline solution, 51.1 $\pm$ 7.3.

Complete blood counts done on guinea pigs after prolonged and repeated administration of the plasma substitutes in question did not reveal alterations of known significance.

Histologic studies of certain organs of guinea pigs after prolonged and repeated administration of the plasma substitutes did not reveal alterations attributable to the replacement fluids when compared with the findings on tissues of normal guinea pigs.

These replacement fluids appeared to have no deleterious effects on the normal growth and development of guinea pigs receiving prolonged and repeated administrations of the fluids under study.

Sensitivity to Periston was not found in rabbits or guinea pigs receiving this substance intravenously.

Utilizing the Clark window in the rabbit's ear, a leukotactic response was seen after the intravenous administration of Dextran. A leukotactic response was not found after the administration of Plasmoid or Periston.

Conclusions

1. Plasmoid, Dextran Ph and Periston, by the criteria used in this study, have been found to be satisfactory replacement fluids for blood lost by hemorrhage in albino rats, guinea pigs and dogs.

2. Deleterious or noxious effects were not observed after the administration of these replacement fluids in experimental animals.

Acknowledgments

For assistance in the interpretation of the electrocardiograms, we are indebted to Drs. H. B. Burchell and R. J. Boucek. For the final evaluation of the microscopic slides of the guinea pig tissues we wish to thank Drs. A. H. Baggenstoss and A. G. Karlson. The technical assistance of Mr. Walter Ogg is gratefully acknowledged.

References

[1] Hamilton, J. I., Hoar, W. S., and Haist, R. E.: A comparison of the efficacy of different infusion media in shock. Canad. J. Research, Sect. E. **24:** 31, 1946.

[2] Locke, W.: An experimental method for evaluating blood substitutes; report on saline, plasma, polyvinyl alcohol and isinglass. Science **93:** 475, 1944.

[3] Scott, C. C., Worth, H. M., and Robbins, E. B.: Comparative value of some blood substitutes used for treatment of experimental shock. Arch. Surg. **49:** 315, 1944.

[4] Figueroa, L., and Lavieri, F. J.: The use of pectin and other agents to prevent shock. Surg., Gynec. & Obst. **78:** 600, 1944.

[5] Mann, F. C.: Shock and haemorrhage: an experimental study. Surg., Gynec. & Obst. **21:** 430, 1915.

[6] Kendrick, D. B., Jr.: Results of intravenous and intra-arterial administration of fluid in traumatic shock produced experimentally. Surgery **6:** 520, 1939.

[7] Rosenthal, S. M.: Experimental chemotherapy of burns and shock. IV. Production of traumatic shock in mice. V. Therapy with mouse serum and sodium salts. Pub. Health Rep. **58:** (pt. 2) 1429, 1943.

[8] Swingle, W. W., Kleinberg, W., and Hays, H. W.: A study of gelatin and saline as plasma substitutes. Am. J. Physiol. **141:** 329, 1944.

[9] McKee, F. W., Laycock, C. F., Martens, T. G., and Nicholl, R. J.: Hemorrhagic shocks; the relative effect of saline, washed red cells, and heparinized plasma in dogs. Surg., Gynec. & Obst. **5:** 509, 1944.

[10] Wiggers, H. C., Ingraham, R. C., and Dille, J.: Hemorrhagic-hypotension shock in locally anesthetized dogs. Am. J. Physiol. **143:** 126, 1945.

[11] Wiggers, C. J., and Werle, J. M.: Exploration of method for standardizing hemorrhagic shock. Proc. Soc. Exper. Biol. & Med. **49:** 604, 1942.

[12] Glasser, O., and Page, I. H.: Experimental hemorrhage shock; a study of its production and treatment. Am. J. Physiol. **154:** 297, 1948.

[13] Gregerson, M. I.: A standard method of producing shock in dogs by a single massive hemorrhage. Proc. Soc. Exper. Biol. & Med. **55:** 272, 1944.

[14] Hamilton, A. G., Parkins, W. M., and Waltzer, F.: A comparison of ten infusion fluids in the treatment of moderate and severe hemorrhage in animals. Am. J. Physiol. **150:** 641, 1947.

[15] Arimoto, F., Necheles, H., Levinson, S. O., and Janota, M.: Hemorrhagic shock; method for its production and formula for prognosis. Am. J. Physiol. **143:** 198, 1945.

[16] Henderson, Y., and Haggard, H. W.: Hemorrhage as a form of asphyxia. J. A. M. A. **78:** 697, 1922.

[17] Ivy, A. C., Greengard, H., Stein, I. F., Jr., Grodins, F. S., and Dutton, D. F.: The effect of various blood substitutes in resuscitation after an otherwise fatal hemorrhage. Surg., Gynec. & Obst. **76:** 85, 1943.

[18] Lawson, H.: The measurement of bleeding volume in the dog for studies on blood substitutes. Am. J. Physiol. **140:** 420, 1943.

[19] —, and Rehm, W. S.: The relative value of various fluids in replacement of blood lost by hemorrhage, with special reference to the value of gelatin solutions. Am. J. Physiol. **140:** 431, 1943.

[20] Essex, H. E., and Graña, A.: Behavior of the leukocytes of the rabbit during periods of transient leukopenia variously induced. Am. J. Physiol. **158:** 396, 1949.

[21] Pender, J. W., and Essex, H. E.: A study of traumatic shock under certain anesthetics. Anesthesiology **4:** 247, 1943.

The Flicker Fusion Frequency and Its Response to Nitroglycerin in Normal Subjects and in Patients with Cardiovascular Disease

By ANCEL KEYS, PH.D., AND ERNST SIMONSON, M.D.

Krasno and Ivy have claimed that the change after sublingual nitroglycerin in the frequency at which a flickering light appears to fuse (f.f.f.) sharply differentiates between cardiovascular normals and patients with coronary and/or hypertensive disease and that this test may be useful in detecting and evaluating such disease. On the basis of a detailed analysis of the original publication and of data on 304 men these claims are denied. Indications for further study of flicker phenomena are discussed and fiducial norms are presented.

THE FUSION frequency (or critical frequency) of flicker is that rate of successive light flashes where the sensation of flicker disappears and becomes the same as that of continuous light. There is reason to believe that the fusion frequency of flicker (f.f.f.) in a subject with normal ocular structures depends on the time parameter of excitability of the visual pathways,[1, 2] primarily of the visual centers.[3–5] While the literature on the flicker phenomenon goes back over a period of one hundred years, the application to physiologic or clinical stress situations is quite recent. Simonson and co-workers[6] found a decrease of the fusion frequency of flicker in fatigue of the central nervous system and in various types of pathology, among others in a group of 21 patients with heart disease.[7] This seemed to be in harmony with observations on the fatigability of cardiac patients in mental as well as in physical work, but no suggestions were made as to the potential value of this method for diagnosis or prognosis of cardiac disease.

Recently, Krasno and Ivy[8] have reported studies on the fusion frequency of flicker before and after the sublingual administration of 0.4 mg. of nitroglycerin and stated, "We believe our results clearly show that the nitroglycerin-flicker test has revealed the presence of arterial hypertonus or spasm of the retinal arteries in 99 per cent of patients with existing hypertension or coronary arterial disease" (p. 1274). Further, they suggest that "the nitroglycerin-flicker test may prove to be a valuable diagnostic aid (a) for the presence of angina pectoris and coronary occlusion where the evidence is equivocal, (b) for the detection and management of persons who may later develop hypertension and coronary arterial disease" (p. 1275).

It is the purpose of the present article to examine these views and to present new data with a critical statistical analysis.

ANALYSIS OF THE KRASNO AND IVY REPORT

Krasno and Ivy make the basic assumptions, as a working hypothesis, that there is hypertonus or spasm in hypertension and in coronary arterial disease, that this condition is reflected in the retinal vessels, that the hypertonus or

From The Laboratory of Physiological Hygiene, University of Minnesota, and The Veterans Administration Hospital, Minneapolis, Minn.

This work was supported in part by the Research Grants Division of the United States Public Health Service.

Published with the approval of the Chief Medical Director, Veterans Administration Hospital. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

spasm in the retinal vessels tends to be relieved by nitroglycerin, and that the tonus of the retinal vessels is indicated by the fusion frequency of flicker. However, Krasno and Ivy did not actually study the retinal vessels and do not even mention eyeground findings in their patients and subjects, the whole chain of reasoning being dependent simply on the observed response of the flicker fusion frequency to nitroglycerin.

Weekers and Roussel[1] found that changes in the retinal vessels can be seen with the ophthalmoscope before there is a change in the fusion frequency of flicker. Even in patients with marked arteriosclerotic changes in the retinal vessels (grade III), the fusion frequency was usually only slightly below normal. It might be inferred, therefore, that the ophthalmoscope would be a better discriminator in these regards than the flicker apparatus. However, the clinical value of the nitroglycerin-flicker test is not necessarily dependent on the theory offered by Krasno and Ivy. The real question is the extent to which their test discriminates between diseased and healthy persons, and its possible use in predicting the appearance of frank disease in persons who are clinically healthy or who present an equivocal picture.

Krasno and Ivy reported findings on four groups: (1) 32 "normal," clinically healthy persons between 20 and 50 years of age (mean age 27.8 years); (2) 268 "patients without evidence of cardiovascular disease"; (3) 216 patients with hypertension and/or coronary heart disease; and (4) 20 cardiac patients without evidence of hypertension or coronary disease. The sex composition of none of the groups was specified and the only information about the age in group 3 was the ranges of the clinical categories. Comparisons are somewhat hindered by the fact that the fusion frequency was reported in flashes per second for the "normal" subjects and in flashes per minute in the three categories of patients. Here we shall convert all data to flashes per second in keeping with the consistent practice in the previous literature.

No nitroglycerin tests were reported on the clinically healthy subjects but it was stated that they had a mean flicker fusion frequency of 44.5 flashes per second without the drug. The only relevance of this group seems to be to demonstrate that patients with hypertension or coronary disease tend to have low values for the fusion frequency of flicker. However, the patients without evidence of cardiovascular disease also had values of the fusion frequency quite comparable with those for the cardiovascular patients, except the group with malignant hypertension, but definitely lower than for the normal persons of equal age. This is consistent with the known fact that various types of pathology may depress the fusion frequency of flicker.[2, 4, 10, 11]

The real burden of Krasno and Ivy's thesis rests on the comparison in the flicker fusion frequency response to nitroglycerin between the two categories of patients, those with and those without evidence of cardiovascular disease, and it must be noted that the latter were not clinically healthy or "normal." Among these 268 patients who were considered as "cardiovascular normals," the sublingual administration of 0.4 mg. nitroglycerin was followed by no change or a decrease in fusion frequency in 206 patients and an *increase* in 62 patients. It was concluded that a decrease in fusion frequency is the "normal" response, and that an increase is an "abnormal" response. This conclusion apparently reflected the preponderance of responses and the fact that among the "abnormal" responders, papaverine or a second dose of nitroglycerin may produce a "normal" change (decrease) in fusion frequency of flicker. However, there is no mention of the effects with papaverine or a second dose of nitroglycerin in the patients who initially gave "normal" responses. Finally, it should be mentioned that papaverine treatment of 60 cardiovascular patients was followed by "normal" responses to the nitroglycerin-flicker test.

In contrast, all of the patients with hypertension or coronary heart disease responded to nitroglycerin with an increase in flicker fusion frequency. The type of pathology and the clinical picture did not seem to influence the magnitude of the change in fusion frequency. Among the 20 patients with cardiovascular disease but without evidence of hypertension

or coronary disease, one patient (Buerger's disease) showed an increase in fusion frequency after nitroglycerin.

The data provided by Krasno and Ivy obviously provide no more than a suggestion that the flicker fusion response to nitroglycerin may have real diagnostic utility. The lack of tests on true "normals" for comparison, the variable results in the reference group of patients without evidence of cardiovascular disease, and the absence of statistical analysis are notable. We have attempted to remedy these defects in the studies reported below.

Methods and Materials

The fusion frequency of flicker was determined by means of a newly developed electronic apparatus,[12] which provides for the controlled variation of the brightness and of the light:dark ratio in addition to variation of the frequency.

The conditions of Krasno and Ivy's arrangement were reproduced as closely as possible. There was a slight difference in the color of the light source but this is considered to be without consequence. In the range of illumination used here, the color, when tested at the same brightness level, does not affect the fusion frequency of flicker.[13] The electronically produced light flashes approach the ideal square wave form more closely than light flashes produced by mechanical interruption through rotating disks or cylinders, such as used in Krasno and Ivy's apparatus; it is inconceivable that such a difference would affect the results. Evidence of the degree to which we approximated Krasno and Ivy's procedure is a comparison of the normal means. The mean fusion frequency of Krasno and Ivy's group of 32 normal subjects from 20 to 50 years (mean age 27.8 years) was 44.5 flashes per second, and that of our group of 58 normal men from 48 to 58 years was 43.1 flashes per second. The slight difference is consistent with the known facts of the age trend.[14, 15]

The majority of our measurements were made in the sitting position but in some of our subjects the fusion frequency was measured in the supine position. The glow modulator tube in which the flicker is generated in our apparatus can be adjusted readily to any angle. There were two reasons for introducing the body position as a variable. First, it is known[16] that the hemodynamic effect of nitroglycerin is affected by the body position so that a comparison of the supine and the sitting positions might be useful for the analysis of nitroglycerin effects. Second, as a method suggested for differentiation between patients with and without cardiovascular disease, standards should be provided for use at the bedside.

After a rest period of 10 minutes or more, the flicker fusion frequency was determined before and four and six minutes after sublingual administration of 0.4 mg. of nitroglycerin. All determinations were made in duplicate; analysis of the duplicate records showed a repeat variability of less than 0.5 flashes per second.

Subjects

A total of 302 men were studied, comprising 47 controls, 145 clinically healthy ("normal") subjects and 110 patients with cardiovascular disease. The normal subjects ranged from 45 to 58 years and the patients were within a similar age range except for a few patients with rheumatic heart disease. The normal men have been under repeated observation in this Laboratory for a period of four years. They were screened as to absence of disease in thorough clinical examinations and various types of stress tolerance tests.[17] Some of the cardiovascular patients were members of the same group who had developed cardiovascular disease in recent years and a few others were referred by private physicians; most of the patients were from the Minneapolis Veterans' Hospital.

Results

The principal results are summarized in table 1. In the first place, dummy trials (controls) without nitroglycerin on 47 men established the repeat variability of the procedure as used in the nitroglycerin tests. The mean change was very close to zero (+0.02) and the standard deviation of the changes was ±0.68, that is in roughly two-thirds of the controls the second measurement of flicker fusion frequency without nitroglycerin was within the range +0.70 and −0.66 flashes per second. The administration of nitroglycerin to the clinically healthy men, both in the supine and in the seated position resulted in substantially identical results; the mean changes from pre- to postnitroglycerin did not differ significantly from the controls.

The same was true of the 58 patients with hypertension (rows 5, 6, 7 in table 1) and the patients with infarcts but without angina (row 9). In a more detailed analysis it was found that the response to the nitroglycerin-flicker test in patients with advanced hyper-

tension was not significantly different from that in patients with only mild to moderate hypertension. However, in the group of patients with angina pectoris (nine patients with a history of infarction and 13 patients with no evidence of infarction) there was a statistically significant (<0.01 probability of chance explanation) tendency to an increase in the fusion frequency of flicker after nitroglycerin.

In addition to the patients summarized in table 1, tests were made in the supine position on three patients with angina pectoris without infarction and on two patients with infarction

TABLE 1.

The flicker fusion frequency (f.f.f.) and its response (Δ) to nitroglycerin. The controls were subjected to a dummy experiment, omitting the nitroglycerin. All values in flashes per second. S. D. = standard deviation.

Group	Position	No. Men	f.f.f.		Δ	
			Mean	S.D.	Mean	S.D.
1. Control	Seated	47	42.3	2.02	+0.02	0.68
2. Healthy	Supine	87	46.7	3.40	−0.13	1.28
3. Healthy	Seated	58	43.1	2.20	+0.14	0.86
4. 2. + 3.	—	145	—	—	−0.02	1.14
5. High B. P.	Supine	23	47.8	3.57	−0.17	1.46
6. High B. P.	Seated	35	41.9	3.50	+0.17	1.85
7. 5. + 6.	—	58	—	—	+0.04	1.70
8. Angina	Seated	22	39.8	3.55	+1.90	2.41
9. Infarct, without Angina	Seated	7	41.1	5.56	−0.06	1.69

but no angina; their responses to the nitroglycerin-flicker test were within the normal limits as calculated from the data in line 2, table 1. Finally, tests were made on 10 patients with rheumatic heart disease (mostly with some degree of failure) and on seven patients with miscellaneous abnormalities in the electrocardiogram; all of these patients were likewise within the limits of the normal response.

The variability (S. D.) between the pre- and postnitroglycerin fusion frequency was somewhat greater than between the first and second tests in the control series. This means that in healthy men nitroglycerin administration introduces variable factors, probably in the blood supply to the visual pathways; this would be compatible with the rather complex circulatory situation after nitroglycerin.

Table 1 indicates that the variability of the change after nitroglycerin (ΔS. D.) was higher in all groups of patients than in normal men. Table 2 shows that these difference in the variability, tested by the F test, were statistically significant. This fact that nitroglycerin produces more variable results in patients than in healthy men has the result of interfering with the reliability of differentiation, with the nitroglycerin-flicker test, between healthy men and men with, for example, coronary insufficiency.

It was noted above that the response to the nitroglycerin-flicker test was substantially identical in the seated and in the supine positions. However, without nitroglycerin, that is in the initial measurement, the fusion frequency of flicker was lower in the seated position in both healthy men and in men with hypertension. This difference is statistically highly significant in both groups ($p = < 0.01$). In a few trials with patients with angina pectoris and with myocardial infarcts a similar effect of posture was observed. These results suggest that in all persons there may be a more effective cerebral circulation in the supine than in the sitting position.

TABLE 2.

Comparison of 58 "normal" men with the several categories of patients in regard to the variability, in the seated position, of the change in flicker fusion frequency after nitroglycerin. VR = variance ratio, patients:normals.

Patients	No.	VR	Signif.
High B. P.	35	4.66	<0.01
Angina	22	7.90	<0.01
Infarct, no angina	7	4.10	<0.01

The means of the initial flicker fusion frequency in patients with arterial hypertension were not significantly different from those of the healthy subjects. However, when only patients with advanced hypertension were considered, the initial fusion frequency was significantly subnormal (mean = 39.1 flashes per second in seven patients in the seated position). The mean initial flicker fusion frequency was also distinctly subnormal in patients with angina pectoris as indicated in table 1. In 10 patients with rheumatic fever

heart disease, the initial flicker fusion frequency was markedly subnormal, the mean for seven patients in the supine position and three patients seated being only 36.8; most of these patients were in failure. This is in harmony with the earlier finding that the fusion frequency tends to be low in severe circulatory disorders, presumably because of relative cerebral hypoxia or ischemia.[7]

So far, we have discussed group means and general variability. This does not precisely answer the question as to the differentiation of individuals. Krasno and Ivy arrived at their conclusion that the nitroglycerin-flicker test differentiates 99 per cent of patients with hypertensive or coronary heart disease from the incidence of changes in the flicker fusion frequency without regard to their magnitude. A more valid procedure would be the comparison of the response of each individual patient with the normal range limits of the response in healthy persons.

Table 3 shows the expected range limits for 95 per cent and for 98 per cent of a normal (healthy) population corresponding to the men included in lines 2 and 3 of table 1. For example, consider a man tested in the seated position who had an initial flicker fusion frequency of 37.5 and after nitroglycerin a value of 39.0. In healthy persons an initial value this low would be expected in less than 1 in 100 men but an increase of this magnitude after nitroglycerin would be expected in more than 5 per cent of healthy men; a reasonable conclusion would be: "initial value probably subnormal, response to nitroglycerin normal."

TABLE 3.

Expected range limits of the flicker fusion frequency for 95 per cent and for 98 per cent of healthy men between 45 and 48 years of age. Values in flashes per second.

Position	Initial		Δ after Ng.	
	95%	98%	95%	98%
Seated.....	38.8 to 47.4	38.0 to 48.2	−1.5 to +1.8	−1.9 to +2.2
Supine.....	40.0 to 53.4	38.8 to 54.6	−2.6 to +2.4	−3.1 to +2.9

TABLE 4

Numbers and percentages of patients with cardiovascular disease who exceeded the expected range limits of 95% and of 98% of a healthy population in the initial flicker fusion frequency and in the response to nitroglycerin (Δ Ng.). "ECG only" comprises men with abnormal electrocardiograms without evidence of infarction and without clinical symptoms.

Group	Total	Initial f.f.f.				Δ after Ng.			
		95%		98%		95%		98%	
		Low	High	Low	High	Decr.	Incr.	Decr.	Incr.
Hypertension, No.....	58	9	2	4	2	6	5	3	2
Per cent.....	100	15.5	3.5	7.0	3.5	10.3	8.6	5.2	3.5
Coronary, No.....	35	17	1	12	1	1	12	1	10
Per cent.....	100	48.6	2.9	34.3	2.9	2.9	34.3	2.9	28.6
Rheumatic, No.....	10	7	0	7	0	1	1	0	0
Per cent.....	100	70.0	0	70.0	0	10.0	10.0	0	0
E.C.G. only, No.....	7	2	0	2	0	1	0	0	0
Per cent.....	100	28.6	0	28.6	0	14.3	0	0	0

The numbers and percentages of our patients outside of these limits are shown in table 4; the values for each patient were compared with the range limits for the position in which he was tested. Attention should be directed first to the right hand side of table 4 which gives the results of the nitroglycerin test.

Only two out of 58, or 3.5 per cent, of the patients with arterial hypertension showed a definitely "abnormal" ($p = 0.01$) response in the sense used by Krasno and Ivy while the incidence of excessive decreases is, if anything,

somewhat greater. This means that the criterion of an increased fusion frequency in the nitroglycerin-flicker test failed to differentiate from healthy men more than 95 per cent of our patients with arterial hypertension. Moreover, after nitroglycerin only 8.6 per cent of these patients showed increases which would be labeled "possibly abnormal"; 5 per cent of a healthy population would be so classed.

The results of this analysis are somewhat more favorable in the patients in the coronary heart disease group (angina pectoris, myocardial infarct, or both). But even here the nitroglycerin-flicker test failed to differentiate 70 per cent of the patients from healthy men. Substantially the same result obtained when the men with angina and those with infarcts were considered separately.

For the 93 combined patients with hypertension or coronary heart disease a probably significant increase in flicker fusion frequency after nitroglycerin was found in 12 men, while an equally significant decrease was found in four men. The criterion of a probably significant increase was met by less than 13 per cent of the patients and that of a possibly significant increase by only 18 per cent of these patients.

The left side of table 4 shows the numbers and percentages of patients who fall outside of the normal range limits of the fusion frequency of flicker without nitroglycerin administration. The incidence of apparent abnormality in this regard is more impressive than the change after nitroglycerin. All of the patient groups show significant incidences of patients with low fusion frequencies, this being least striking in the patients with hypertension and most notable in the patients with valvular heart disease. In the combined 93 hypertension-coronary disease patients, 16 are below the low limit for 99 per cent of healthy men and 26 men fall in the "possibly subnormal" class.

These results suggest that the simple flicker fusion frequency measurement is at least as good as, and very possibly it is better than, the nitroglycerin-flicker test in the differentiation of hypertensive and coronary disease from the healthy state. We have tested the statistical significance of the differences, apparent in table 4, between the criterion of low fusion frequency and the criterion of increase after nitroglycerin as devices to differentiate patients from healthy men. The difference in favor of the simple flicker fusion frequency test could arise by chance in roughly one out of six trials.

Discussion

A full explanation of the difference between our results and those reported by Krasno and Ivy cannot be offered. One obvious factor is the great disparity between the findings on our group of healthy men and their findings on their reference group, that is patients without evidence of cardiovascular disease. We cannot agree that a decrease or no change in the fusion frequency of flicker after nitroglycerin is the "normal" response since we found that an increase was as frequent as a decrease in these healthy men. It could be suggested, of course, that a decrease is characteristic of *sick* people who do not show evidence of major cardiovascular disease. In any case it is difficult to understand the justification in discarding the results on 62 of the "cardiovascular normals" of Krasno and Ivy simply on the ground that they did not conform to the majority findings.

The difference between our findings and those of Krasno and Ivy on cardiovascular patients is more puzzling. They reported a *uniform* increase in the fusion frequency of flicker after nitroglycerin in this category. We found a *tendency* in this direction in patients with angina pectoris, but it was very far from being uniform. And in hypertension there was not even a tendency to increase. The majority of our patients were not very ill and it is possible that the patients studied by Krasno and Ivy represented, on the average, more advanced stages of disease, but it is inconceivable that the clinical status of the two series did not overlap to a considerable extent.

The most important question raised by Krasno and Ivy is the possible value of the nitroglycerin-flicker test for the early detection of cardiovascular disease, particularly at the subclinical stage. We were unable to discover the slightest support for this view in our own

work. Although we found some patients who had a considerable increase in flicker fusion frequency after nitroglycerin, these were few and represented, in general, well established cardiovascular disease.

Krasno and Ivy reported no analysis of the magnitude or significance of change in the flicker fusion frequency after nitroglycerin and apparently considered only the *direction* of change. In our own series, if no account is taken of the magnitude or significance of the change, it is found that a considerable proportion of the patients *did* have higher values for the fusion frequency after nitroglycerin. But a considerable proportion of our healthy men also had higher values after nitroglycerin and even in the control series, where no nitroglycerin was administered, 44.7 per cent of the second fusion frequency measurements were above the initial fusion frequency. Table 5 summarizes the data analyzed in this way.

There are obviously no significant differences between the controls, the healthy men, or the men with hypertension, in the percentages of "abnormal" responses in the sense used by Krasno and Ivy. Statistical tests showed, likewise, that there is no significant difference between the incidence of "abnormal" responses in the healthy men and the combined group of those with hypertension or coronary disease. Only the patients with angina pectoris differed significantly from the healthy men in the incidence of the so-called abnormal response. The difference in this latter case is small, however; with equal numbers of angina patients and of healthy men there would be only 1.3 times as many "abnormal" responses in the patients as in the healthy men.

In our hands, at least, the nitroglycerin test is completely useless in discriminating hypertensive patients from healthy men; random guesswork would serve equally well. But it is useful to see what results we should expect, using the criterion of "abnormality" proposed by Krasno and Ivy, in discriminating patients with angina pectoris from healthy men in a mixed group presented for diagnosis.

For this purpose we may use the simple computation procedure recently applied (Keys[18]) to another proposed discrimination device. Suppose we have a population made up of 900 healthy men and 100 men with coronary insufficiency. The nitroglycerin-flicker test will result in finding "abnormal" responses (that is, increases, as in table 5) in $0.43 \times 900 + 0.74 \times 100 = 461$ men, of whom only 74 would actually be diseased. There would be 26 diseased men missed and 387 healthy men incorrectly labeled "coronary disease." There would be 415 diagnostic errors in "finding" the 74 diseased men.

It may be suggested, of course, that some of the "healthy" men used in the present studies are actually unrecognized cases of coronary disease and therefore the true incidence of "abnormal" responses in completely healthy men is less than we found. While this is conceivable, it is inconceivable that undiscovered or latent coronary disease exists in more than a small fraction of our men who were pronounced "healthy" after prolonged observation and very elaborate tests and measurements. But, suppose that 10 per cent of our healthy men are actually cases of latent coronary disease and that such latent cases have the same response to the nitroglycerin-flicker test as the men with frank angina pectoris. We can then calculate the incidence of abnormal responses in truly healthy men as follows.

Among 1000 men clinically considered to be healthy, there would be 100 who are hidden cases of coronary disease and of these latter there would be 74 men who would have an "abnormal" response to the Krasno-Ivy test. But in the entire 1000 men there would be 430

TABLE 5.

Percentages of men who had lower (−), no change (0), and higher (+) values for flicker fusion frequency after nitroglycerin (or in the dummy second trial in the controls) than in the initial measurements.

Category	−	0	+
1. Controls	42.6	13.7	44.7
2. Healthy	39.7	17.2	43.1
3. Hypertension	42.9	11.4	45.7
4. Angina	21.7	4.4	73.9
5. 3. + 4.	34.4	8.7	56.9

abnormal responders, of whom 430 − 74 = 356 would be in the 900 truly healthy men. The percentage of abnormal responses among truly healthy men would then be 100 × 356/900 = 39.5.

We may now repeat the computation to find the results of application of the Krasno-Ivy test with this revised estimate for healthy men. In a population of 1000 men made up of 900 truly healthy men and 100 cases of latent coronary disease we would "find" 74 of the 100 diseased men and would erroneously apply the label "coronary disease" to 320 of the 900 truly healthy men. There is a total of 346 diagnostic errors, or a ratio of roughly five errors to each correctly positive diagnosis. The foregoing computation is, we believe, the most favorable estimate for the validity of the test we can make.

From table 5 it is indicated that the simple measurement of flicker fusion frequency without nitroglycerin is not inferior to the Krasno-Ivy test as a means of discriminating patients from healthy men. With the simple measurement of fusion frequency alone the criterion is a subnormal value for flicker fusion frequency.

Independent of any factor of disease or effect of nitroglycerin, there will be, of course, a tendency for low values of the initial fusion frequency to be associated with increases after nitroglycerin. This follows from the fact that there is a random "error" in such measurements, partly from true error in measurement and partly from random fluctuations in the ability of the subject to see and report correctly the fusion point. If the initial fusion frequency measurement happens, by such random error, to be lower than the subject's true mean fusion frequency, the chances are that a succeeding measurement will be higher (law of the tendency toward the mean).

Among the increases (and decreases) after nitroglycerin there must be at least some artefacts of this kind. Their frequency and importance may be estimated with the help of the data in the control series when no nitroglycerin was given. We have calculated, by least squares, the value of the slope b in the regression equation, $y = a + bx$, where y = the change in flicker fusion frequency after nitroglycerin and x = the prenitroglycerin flicker fusion frequency. For the control series $b = -0.108$ and this is statistically highly significant. The alternative calculation of the correlation coefficient gave a value of $r_{x,y} = -0.32$ for this control series. Similar calculations with the data for the patients with hypertension and with angina pectoris gave values for b of -0.177 and 0.198, respectively. These slopes prove to be not significantly different from that in the control series. In other words, the inverse correlation between the initial flicker fusion frequency and the change after nitroglycerin in these series may be explained by the regression toward the mean observed in the control series.

TABLE 6.

Incidence of "abnormal" flicker fusion frequency results (outside the 98 per cent normal range limits) in men with coronary disease. "Initial" = subnormal value before nitroglycerin, Δ f.f.f. = abnormal rise after nitroglycerin.

Category	Total Men	Initial	Δ f.f.f.	Both
Angina	16	2	6	1
Infarct	19	10	4	4
Total	35	12	10	5

This relative absence of correlation suggests that the initial flicker fusion frequency and the response to nitroglycerin are relatively independent criteria for discriminating between coronary patients and "normals" and might, therefore, be combined to yield a more effective discrimination. In table 4 it was noted that out of 35 coronary patients there were 12 men who showed significantly subnormal values for the initial fusion frequency and 10 men who showed significant increases in fusion frequency after nitroglycerin. On inspection of the data, however, it was found that only five of these men were abnormal in *both* regards and that a total of 17 of these 35 coronary patients were significantly abnormal with one or the other criterion. If both criteria are applied, with the 98 per cent limits given in table 3, we find that 48.5 per cent, instead of 28.6 per cent, of the coronary patients are

abnormal in the sense that they differ from 99 per cent of clinically healthy men.*

In the course of tabulating the data on the coronary patients for the analysis with both criteria (that is, initial fusion frequency and Δ fusion frequency after nitroglycerin), it was observed that the patients with angina but without evidence or history of infarction appeared to behave differently from the patients with infarcts. The men with angina but without infarcts tended to be more abnormal in response to nitroglycerin than in their initial flicker fusion value. On the other hand, the men with infarcts tended to be more abnormal initially than in their response to nitroglycerin.

The data which are summarized in table 6 were treated statistically by the exact contingency analysis[19] from which it was found that the probability of chance explanation of the differential behavior of "angina" and "infarcts" summarized in table 6 is only 0.04799; the cruder chi square approximation gave a value of 0.03 for this probability. The desirability of further research along these lines is obvious.

It will be recalled that Krasno and Ivy began their study of the nitroglycerin-flicker test on the theory that vasospasm, which would be relieved by nitroglycerin, may be present in cardiovascular patients. The findings here give no support to this theory except, perhaps, in the patients with angina pectoris. There is certainly no evidence from these data for vasospasm in the hypertensive patients, much less that vasospasm, discernible by this method, may precede the appearance of clinical hypertension.

Finally, it is well to point out that the strictures on the utility of the nitroglycerin-flicker test for discovering cardiovascular disease do not mean that flicker fusion frequency measurements have no utility in studying patients with suspected or actual circulatory disorders. So far as it goes, the data here confirm previous findings that the fusion frequency of flicker is sensitive to deficiencies in the circulation, particularly that of the brain.

* Note that with the 98 per cent limits there will be 1 per cent beyond each end of the range.

Summary

1. An analysis has been made of the report by Krasno and Ivy that the response of the flicker fusion frequency (f.f.f.) to sublingual nitroglycerin differentiates cardiovascular patients with hypertension or coronary disease from persons who are clinically healthy or normal.

2. Data are reported on the flicker fusion frequency before and after nitroglycerin in 145 clinically healthy, "normal" men and in 110 men with cardiovascular disease. Data are given also on 47 men who served as controls in dummy experiments. Studies were made both in the seated and in the supine position.

3. Fiducial tables are presented for the range limits of the initial flicker fusion frequency and its change after nitroglycerin within which it is predicted 95 per cent and 98 per cent of clinically healthy, "normal" men will be found.

4. The claim that the Krasno-Ivy nitroglycerin-flicker test may be a useful discriminator for detecting or evaluating hypertensive or coronary disease is not confirmed.

5. In clinically healthy men increases in flicker fusion frequency after nitroglycerin were just as frequent as were decreases and a similar result was obtained with patients with hypertension.

6. About 30 per cent of patients with coronary disease showed a significant increase in flicker fusion frequency after nitroglycerin. An equal, or larger, percentage of these patients showed prenitroglycerin fusion frequency values which are significantly subnormal.

7. All categories of men showed higher fusion frequency values in the supine position than in the upright position but the response to nitroglycerin was substantially the same in both positions.

8. The present data and analysis indicate that the simple flicker fusion frequency measurement is not inferior to the nitroglycerin-flicker test in differentiating cardiovascular disease and that neither test can be recommended as a screening or detecting device for individuals.

9. The possibilities of using both initial

flicker fusion frequency and the change after nitroglycerin as discriminating criteria are discussed.

ACKNOWLEDGMENTS

We are grateful to Dr. Austin Henschel for aid in some of the flicker measurements, and to Mr. Kenneth Tiede for some of the computations.

REFERENCES

[1] CROZIER, W. J., AND WOLF, E.: Theory and measurement of visual mechanism. VI. Wavelength and flash duration in flicker. J. Gen. Physiol. **25:** 89, 1941.

[2] SIMONSON, E.: Fatigue of the central nervous system. Clin. Proc. **2:** 112, 1943.

[3] HALSTEAD, W. C., KNOX, G. W., AND WALKER, A. E.: Modification of cortical activity by means of intermittent photic stimulation in the monkey. J. Neurophysiol. **5:** 349, 1942.

[4] SIMONSON, E., FOX, M. S., AND ENZER, N.: Influence of vestibular stimulation on the fusion frequency of flicker. Arch. Otolaryngol. **38:** 245, 1943.

[5] IRELAND, F. H.: A comparison of critical flicker frequencies under conditions of monocular and binocular stimulation. J. Exper. Psychol. **40:** 282, 1950.

[6] SIMONSON, E., ENZER, N., AND BLANKSTEIN, S. S.: Measurement of fusion frequency of flicker as a test for fatigue of the central nervous system. J. Indust. Hyg. & Toxicol. **23:** 83, 1941.

[7] ENZER, N., SIMONSON, E., AND BLANKSTEIN, S S.: Fatigue of patients with circulatory insufficiency, investigated by means of the fusion frequency of flicker. Ann. Int. Med. **16:** 701, 1942.

[8] KRASNO, L. R., AND IVY, A. C.: The response of the flicker fusion threshold to nitroglycerin and its potential value in the diagnosis, prognosis, and therapy of subclinical and clinical cardiovascular disease. Circulation **1:** 1267, 1950.

[9] WEEKERS, R., AND ROUSSEL, F.: La mesure de la fréquence de fusion in clinique. Docum. Opthalmol. **2:** 130, 1948.

[10] ENZER, N., SIMONSON, E., AND BLANKSTEIN, S. S.: The state of sensory and motor centers in patients with hypothyroidism. Ann. Int. Med. **15:** 669, 1941.

[11] SIMONSON, E., KEARNS, W. N., AND ENZER, N.: Effect of oral administration of methyl testosterone on fatigue of eunuchoids and castrates. J. Endocrinol. **28:** 506, 1941.

[12] FRITZE, C., AND SIMONSON, E.: A new electronic apparatus for the measurement of the fusion frequency of flicker. Science **113:** 547, 1951.

[13] HECHT, S., AND SHLAER, S.: Intermittent stimulation by light. V. The relation between intensity and critical frequency for different parts of the spectrum. J. Gen. Physiol. **19:** 965, 1936.

[14] SIMONSON, E., ENZER, N., AND BLANKSTEIN, S. S.: The influence of age on the fusion frequency of flicker. J. Exp. Psychol. **29:** 252, 1941.

[15] BROZEK, J., AND KEYS, A.: Changes in flicker-fusion with age. J. Consult. Psychol. **9:** 87, 1945.

[16] WEISS, S., WILKINS, R. W. AND HAYNES, F. W. Nature of circulatory collapse induced by sodium nitrate. J. Clin. Investigation **16:** 73, 1937.

[17] ANON.: Cardiovascular research at the Laboratory of Physiological Hygiene. Bull. Hennepin County M. Soc. **19:** 39, 1948.

[18] KEYS, A.: "Giant molecules" and cholesterol in relation to atherosclerosis. Bull. Johns Hopkins Hosp. **88:** 473, 1951.

[19] FISHER, R. A. The logic of inductive inference. J. Roy. Stat. Soc. **98:** 39, 1935.

Factors Influencing Cerebral Blood Flow and Metabolism

A Review

By PERITZ SCHEINBERG, M.D., AND HAROLD W. JAYNE, M.D.

The results of studies utilizing the nitrous oxide technic for measuring cerebral blood flow have been reviewed and divided into three groups: (1) those in which cerebral blood flow and metabolism were normal, (2) those in which cerebral blood flow was increased, and (3) those in which cerebral blood flow and metabolism were decreased. The factors which apparently regulate and control cerebral blood flow and metabolism are reviewed and discussed.

THE DEVELOPMENT of the nitrous oxide technic for the determination of cerebral blood flow by Kety and Schmidt in 1945[1] has resulted in considerable clarification of many problems related to the circulation and metabolism of the brain; simultaneously these studies have raised many new questions and opened new vistas for speculation and investigation into the problems of cerebral circulation and metabolism. Prior to the use of this technic, numerous indirect methods of estimating changes in cerebral blood flow had been in use. None was entirely satisfactory, though each made some definite contribution to our knowledge.[2] Direct observations of pial blood vessels through a glass window in the skull had the disadvantages of using animals rather than man, and inferences concerning changes in intracerebral vessels had to be made from observing pial vessels, which may not react similarly to vessels within the brain substance.[3–6] Measurement of arterial-cerebral venous oxygen differences[7,8] is useful in some instances in estimating changes in cerebral blood flow, but no quantitative values can be obtained, and certain alterations in cerebral metabolism will obviate even these estimations. The dye injection method[9] and rate of displacement of spinal fluid[10] are useful procedures; the latter is complicated by the fact that changes in circulation in the skin of the face may directly affect the measurement.

The nitrous oxide procedure is an application of the Fick principle, which states, in effect, that the amount of a substance deposited in an organ in a given period of time is equal to the amount of that substance brought to the organ by the arterial blood minus the amount removed by the venous blood. Cerebral venous blood is obtained from a needle placed in either internal jugular bulb, for the composition of blood in both is essentially the same.[11–13] Arterial blood is obtained from any convenient artery. Blood is drawn from both these sources as the patient breathes a nonanesthetic mixture of nitrous oxide. The final nitrous oxide concentration in the brain is obtained by inference from the cerebral venous nitrous oxide concentration after equilibrium between venous blood and brain has occurred. Cerebral oxygen and glucose consumption are the products of cerebral blood flow and arterial-cerebral venous oxygen and glucose differences respectively. Cerebral vascular resistance is the quotient of mean arterial pressure divided by cerebral blood flow. Cerebral venous oxygen tension can be computed from the per cent oxygen saturation of cerebral venous blood by means of a standard oxyhemoglobin dissociation curve drawn for pH 7.4.

It should be pointed out that the nitrous

From The Department of Experimental Medicine, The University of Miami Medical Research Unit, and the Department of Medicine, Veterans Administration Hospital, Coral Gables, Fla.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

oxide procedure for measuring cerebral blood flow is different from most physiologic applications of the Fick principle in that it measures blood flow per unit weight of brain tissue, and therefore is not dependent upon a knowledge of the weight of the organ. This has certain advantages and disadvantages. One advantage is that determination of brain weight in any given individual would obviously be difficult and unquantitative. A disadvantage is that normal values for cerebral blood flow and metabolism could theoretically be obtained even if a portion of the brain were completely removed, provided that the circulation to and metabolism of the remainder of the brain were still normal.

There has been some discrepancy in the reported normal values for cerebral blood flow. Using a modification of the original nitrous oxide procedure, in which the mean arteriovenous nitrous oxide difference was measured by drawing simultaneous continuous samples from the artery and vein, rather than five separate samples from each, Scheinberg and Stead[14] found a normal mean cerebral blood flow value of 65 ml. per minute per 100 Gm. brain. The reasons for this difference from Kety's reported normal mean value of 54[13] are not entirely clear, and may be due to differences in the technics.

The normal cerebral blood flow represents about 14 per cent of the total cardiac output. The brain extracts considerably more oxygen from the blood flowing through it than does either the liver or the kidney, so that the normal cerebral oxygen consumption is 3.8 ml. oxygen per minute per 100 Gm. brain, or about 53 ml. oxygen per minute for the whole brain.[14] Thus the brain, an organ of only 1400 Gm., accounts for about 22 per cent of the total oxygen consumption of the body. The importance of the brain in the metabolic scheme of the body is even further emphasized by the finding that normal cerebral glucose consumption is 6.2 mg. glucose per minute per 100 Gm. brain, or about 87 mg. glucose per minute for the whole brain. This represents about 70 per cent of the total glucose output of the normal liver.[15] Numerous studies have established that the cerebral respiratory quotient is practically unity,[13, 16] indicating that carbohydrate is the almost exclusive foodstuff of the brain. Although all the oxygen consumed by the brain is apparently utilized in the oxidation of glucose, this oxidation is not complete, and a portion of the glucose is converted to intermediary products, such as lactic and pyruvic acids.[16, 17] Stoichiometrically, the total utilization of 6.0 cc. of oxygen (the normal arterial-cerebral venous oxygen difference) would be accomplished by 8 mg. of glucose. Thus 8 mg. of the 9.9 mg. of glucose (the normal arterial-cerebral venous glucose difference) utilized by the brain can be accounted for by oxidation. The 1.2 mg. of lactic acid and 0.22 mg. pyruvic acid freed by the brain may be considered as representing the anaerobic breakdown of equivalent amounts of glucose. Added to 8 mg. (aerobic consumption), this gives a total of 9.4 mg. of glucose metabolized, which corresponds fairly closely with the measured value of 9.9 mg. Since the brain appears to be incapable of maintaining normal function by energy from the anaerobic breakdown of glucose, a constant supply of oxygen is essential. A constant supply of glucose is also necessary for cerebral cells are apparently able to use only carbohydrates for energy purposes.

The great dependence of brain cells upon a constant and prosperous oxygen environment is well known clinically and cerebral symptoms are prominent in extensive pulmonary disease, at high altitude, or during asphyxia or carbon monoxide poisoning. Apparently certain portions of the brain are able to withstand anoxia better than others, and it appears that the newest areas phylogenetically are most rapidly injured, so that the higher central nervous system functions, such as speaking, thinking, and remembering, are most likely to be permanently impaired by anoxia of short duration. As a matter of fact, unconsciousness usually results in five to seven seconds after complete cessation of cerebral blood flow[18] and anoxia persisting for more than four to five minutes usually results in death, although higher functions may be impaired by much shorter periods of anoxia.

The arterial anatomy of the cerebral circulation is of considerable interest and clinical importance. It consists exclusively of the two internal carotid and vertebral arteries, and

those sources communicate with each other at their entrance into the brain substance in the circle of Willis. It is generally thought that under ordinary circumstances there is little or no exchange of blood among the various sources.[19] Studies have shown that when one of the internal carotids is occluded, the circle of Willis acts as an anastomatic channel, and the blood flow and oxygen consumption on the two sides of the brain remain essentially equal but may both be reduced from normal.[20] The rather high incidence of hemiplegias and other complications following unilateral carotid ligation may be explained by failure of the circle of Willis to function as an anastomatic channel.

Although we are still unable to draw final conclusions concerning all the factors responsible for the regulation of cerebral blood flow and metabolism, we are much farther along in our thinking as a result of studies by the nitrous oxide technic. In addition to gaining specific information about the mechanisms which may regulate cerebral circulation, these studies have granted us further insight into the pathologic physiology of the various disease states studied. For greater clarity these conditions may be divided into three groups: (1) those in which cerebral blood flow and metabolism are unchanged, (2) those in which cerebral blood flow is increased, and (3) those in which cerebral blood flow and metabolism are decreased.

Group I. Cerebral Blood Flow and Metabolism Normal (Table 1)

Apprehension, Artificial Fever, Hyperthyroidism. These will be discussed together, for they all represent states in which cardiac output and total body metabolism are increased. Loose usage of the term *apprehension* in relation to cardiovascular dynamics has resulted in unnecessary confusion. The effects of apprehension on the cardiovascular apparatus will be entirely dependent on the individual's reaction, and general statements, without specific accompanying data, may have no significance. The psychiatric state of acute emotional disturbance defined as apprehension may result in any or all of the following circulatory changes: (1) Tachycardia and increased pulse pressure, with decreased peripheral resistance; this results in an increase in cardiac output of some 40 to 50 per cent and a similar increase in total oxygen consumption.[21] (2) Bradycardia, increased sweating, constriction of skin vessels as characterized by paleness, followed by hypotension, and occasionally, fainting; in this group cardiac output may be below normal.[21] (3) Hyperventilation, associated with changes in the circulation which can no longer be attributed to apprehension per se. Cerebral blood flow studies in a group of normal young men who fell into the first part of the above classification revealed normal values for cerebral blood flow and cerebral oxygen consumption.[14] Under these circumstances, at least, the brain does not share in the increased cardiac output and total oxygen consumption.

Table 1.—*Group I. Cerebral Blood Flow Normal*

	$CMRO_2$*	CVR†
Apprehension	Normal	Slightly Increased
Induced Fever	Normal	Slightly Increased
Hyperthyroidism	Normal	Normal
Essential Hypertension	Normal	Increased
Stellate Block	Normal	Normal
Nicotinic Acid	Normal	Normal
Intravenous Procaine	Normal	Slightly Increased
Histamine	Normal	Decreased
Schizophrenia	Normal	Normal
Insulin Hypoglycemia	Decreased	Decreased
Uremia	Decreased	Normal
Desoxycorticosterone Glucoside	Normal	Normal
Toxemia of Pregnancy	Normal or or Decreased	Increased
20° Head-up Tilt	Normal	Decreased

* $CMRO_2$ = Cerebral oxygen consumption
† CVR = Cerebral vascular resistance

In a group of patients with hyperthyroidism, in whom the mean basal metabolic rate was +54, the average increase in cardiac output was 35 per cent.[22] A similar group of patients showed normal values for cerebral blood flow

and metabolism.[23] This rather surprising finding indicates that the previously accepted belief that cardiac output in hyperthyroidism is increased secondarily to a generalized increased demand of the tissues for blood is probably much too simple. Neither the brain nor the splanchnic area have a low peripheral resistance to act as a stimulus for an increased cardiac output. The finding of a normal cerebral blood flow and metabolism in hyperthyroidism, however, does not further very much our understanding of the psychic manifestations which occur in this disease. Perhaps a series of observations on patients with true psychoses of hyperthyroidism will clarify the issue.

Cardiac output and total body metabolism are greatly increased during induced fever,[24] but cerebral blood flow and metabolism are unchanged in patients with asymptomatic neurosyphilis, and probably normal individuals, during induced fever.[25] It is possible, though no absolute evidence exists to confirm it, that this inability of the brain to increase its metabolism may indicate a relative cerebral metabolic deficiency, and may conceivably account for the delirium which frequently accompanies fever, and even for the aberrant mental behavior seen in some patients with hyperthyroidism. This, however, is at best a conjecture. Until recently, existing evidence indicated that cerebral metabolism normally goes on at its optimal and maximal rate, for those circumstances which increased cardiac output or general body metabolism seemed to have no effect on cerebral circulation and metabolism; however, preliminary studies by Kety and his associates indicate that cerebral metabolism may be increased by injections of epinephrine or muscular exercise.[26]

Essential Hypertension. There is a great increase in cerebral vascular resistance in hypertension uncomplicated by evident renal, cardiac, or peripheral vascular disease, although blood flow and oxygen consumption remain normal.[27] There may be some discrepancy in the reported values for cerebral blood flow in hypertension, for recent observations show a value for cerebral blood flow greater than the value for normal subjects as obtained in that laboratory.[28] This increase in cerebral vascular resistance would appear to be related specifically to an increase in the tone of the cerebral vessels, since none of the other factors known to alter cerebral vascular resistance appear to be operative in this disease. It appears to be rather a reflection of a uniform increase in vascular tone throughout the body. The mechanism for this increase in vascular tone is still unidentified, but studies have indicated that the increased tone can be at least partially relaxed by a drop in arterial pressure, whether such a reduction in pressure is produced by differential spinal sympathetic block,[29] dihydroergocornine,[30] head-up tilt,[28] or thoracolumbar sympathectomy.[31] There is no satisfactory explanation for the observation that cerebral vascular relaxation is not sufficient to maintain normal blood flow following differential spinal block, whereas a normal blood flow is maintained during the reduction in blood pressure resulting from the administration of dihydroergocornine.

Stellate Ganglion Block, Intravenous Nicotinic Acid and Procaine. Unilateral or bilateral stellate ganglion block with procaine produces no alteration in cerebral blood flow, metabolism, or vascular resistance in normals, subjects with essential hypertension, with cerebral vascular disease, and most types of acute cerebral vascular accidents.[32, 33] Recent studies suggest that bilateral stellate ganglionectomy may reduce cerebral vascular resistance in patients with parkinsonism.[34] Interpretation of the statistical analyses of these last data, however, remains somewhat controversial. These studies throw some doubt on the concept that the sympathetic innervation of brain vessels plays a significant role in regulation of cerebral blood flow and also casts considerable doubt on the role of cerebral vascular spasm in the pathogenesis of most varieties of cerebral vascular accidents. Certainly these findings would indicate that stellate block has, at best, a questionable role in the treatment of most types of vascular accidents. It should be pointed out that young patients with cerebral embolisms have not been included in the above studies, and statements concerning the efficacy of stellate block in such subjects cannot be made. Nicotinic acid also produces no change in

cerebral blood flow, even when administered intravenously in large dosage.[35] The intense facial blush produced by nicotinic acid is another reminder that an increase in skin circulation does not necessarily reflect an increase in cerebral circulation. Intravenous procaine in large doses produces no apparent change in cerebral blood flow and may actually increase cerebral vascular tone.[36] Intravenous histamine results in a considerable decrease in cerebral vascular resistance with no change in cerebral blood flow or metabolism.[37] This decrease in cerebral vascular tone may be a response to the fall in arterial pressure resulting from histamine. There is no evidence that this drug has any direct action on cerebral vessels.

Schizophrenia. The finding of normal values for cerebral blood flow and metabolism in schizophrenia[38] does not shed light on the mechanisms regulating cerebral blood flow but does indicate that striking aberrations in mental function may coexist with normal cerebral metabolic values. This is a clinical confirmation of the negative pathologic findings in the brains of schizophrenics.

Insulin Hypoglycemia and Uremia. In both these circumstances cerebral metabolism is reduced even though cerebral blood flow remains normal. In insulin hypoglycemia the mechanism for the reduction in cerebral metabolism appears to be the deprivation of glucose, essential to normal function of cerebral cells. The decreased cerebral vascular resistance which accompanies this condition may be a compensatory effort by the body to provide the needed additional nourishment to the brain. It is not known how long cerebral blood flow would be maintained in a normal range under these circumstances, for the experiments were of an acute nature.[39]

In those patients with uremia who do not have complicating vascular disease, cerebral blood flow and vascular resistance may be normal in association with reduced cerebral metabolism.[40] The lack of correlation between cerebral metabolism and nonprotein nitrogen in these patients suggests that the defect in cerebral oxygen consumption is not due to the presence in the blood of nitrogenous wastes per se, but may be due to the widespread chemical and metabolic disturbances known to occur in uremia.

Desoxycorticosterone Glucoside. The failure of cerebral blood flow and oxygen consumption to change when the cerebral arteriovenous glucose difference and cerebral glucose consumption are greatly decreased following administration of desoxycorticosterone glucoside is of great interest and is difficult to explain.[41] It would indicate that glucose can be "released" from the brain, perhaps from its glycogen stores. These observations lend support to clinical studies on the effects of steroidal hormones on cerebral functions of man.

Toxemia of Pregnancy. Cerebral blood flow remains normal, though there is a great increase in cerebral vascular tone in the toxemias of pregnancy.[42] In the most severe cases, classified as true eclampsia, cerebral oxygen consumption is decreased, apparently due to inability of the cerebral cells to extract normal quantities of oxygen from the blood.

Twenty Degree Head-Up Tilt. The slight decrease in effective cerebral arterial pressure which occurs when a subject is tilted head up twenty degrees is sufficient to relax cerebral vascular tone so that cerebral blood flow remains normal.[43] This differs from the changes resulting from a greater degree of tilting, as will be discussed later.

Group II. Cerebral Blood Flow Increased (Table 2)

Carbon Dioxide (5 to 7 per cent), Diabetic Coma, Anoxia (10 per cent Oxygen). Although only a few conditions exist in which cerebral blood flow has been shown to be increased, through them a great deal has been learned about the mechanisms regulating the flow of blood in the brain. It is not known in what manner the inhalation of 5 to 7 per cent carbon dioxide increases cerebral blood flow (averaging 75 per cent above normal)[44]; it may be a local effect of the carbon dioxide on the vessels themselves, but it is more likely the result of the acidosis (blood pH 7.3) which results. This latter theory is supported by the finding of an increased cerebral blood flow in severe diabetic acidosis, in which there is a decreased blood pH, and a markedly decreased carbon dioxide ten-

sion.[45] There appears to be an excellent correlation between cerebral blood flow and arterial pH in both these circumstances, blood flow increasing as hydrogen ion concentration rises. The association of a decreased cerebral vascular resistance and decreased cerebral oxygen consumption in diabetic coma is further evidence that local brain metabolism has no consistent effect upon cerebral vascular tone. In moderate diabetic acidosis, cerebral blood flow is decreased and cerebral oxygen consumption decreased moderately, but as the acidosis progresses, cerebral blood flow increases even though the patient may be in coma. This seeming paradox is probably the result of the great increase in hydrogen ion concentration in the blood as acidosis progresses, even though carbon dioxide tension progressively decreases. The increased cerebral blood flow resulting from administration of 5 to 7 per cent carbon dioxide should be remembered in the treatment of patients in whom it is desired to speed up the cerebral circulation. Apparently anoxia (administration of 10 per cent oxygen) also has a powerful dilator effect on cerebral vessels,[44] indicating that oxygen tension may play a role in the regulation of cerebral vascular resistance. It is thought that this effect of anoxia upon cerebral vessels is of the greatest clinical importance in the subject's adjustment to relatively acute changes in oxygen environment (such as high altitude); however, further studies at high altitude are necessary to confirm this impression. The administration of oxygen in concentrations above that of room air may actually cause a slight constriction of cerebral vessels.[44]

TABLE 2.—*Group II. Cerebral Blood Flow Increased*

	$CMRO_2$	CVR
CO_2 (5–7%)	Normal	Decreased
Diabetic Coma	Decreased	Decreased
Anoxia (10% O_2)	Normal	Decreased
Anemia of Acute Blood Loss	Normal	Decreased
Cerebral Hemangioma	Normal	Decreased
Papaverine	Normal	Decreased
Thiopental Anesthesia	Decreased	Decreased
Sleep	Normal	Decreased

Anemia of Acute Blood Loss. In the few cases studied, the anemia of acute blood loss appears to cause an increase in cerebral blood flow commensurate to the rise in cardiac output which occurs.[46] This increase in circulation is a compensatory mechanism which maintains a normal state of oxygen delivery and is common to all tissues and organs and not exclusively a property of cerebral vessels. That this compensatory increase does not occur in all types of anemia will be demonstrated later. It is possible that decreased blood viscosity in anemia may account for some of the increase in circulatory rate.

Cerebral Hemangioma. The rapid blood flow in cerebral hemangioma is to be expected and is simply a reflection of the presence of arteriovenous shunting, so that the blood does not pass through cerebral capillaries.[47] Its occurrence is of practical importance in that the measurement of cerebral blood flow may be a diagnostic aid in doubtful cases.

Papaverine. Papaverine, in large doses, apparently has a direct effect on cerebral vessels, resulting in cerebral vasodilatation.[36, 37] The increased cerebral blood flow is an indication that the effect of papaverine is due to more than the fall in arterial pressure which follows its administration.

Thiopental Anesthesia and Natural Sleep. Anesthesia produced by Thiopental results in a 36 per cent decrease in cerebral oxygen consumption, probably indicating a direct depressant effect on the cerebral cells. The slight increase in cerebral blood flow and decrease in cerebrovascular resistance may be completely unrelated to the Thiopental, but due to the increased arterial carbon dioxide tension which occurs in such anesthetized patients.[12] Natural sleep is accompanied by no such alteration in cerebral oxygen consumptions, which remains normal.[48] The slight increase in cerebral blood flow in natural sleep is unexplained, but again may be related to decreased ventilatory exchange and accompanying elevation of arterial carbon dioxide tension.

GROUP III. CEREBRAL BLOOD FLOW DECREASED (TABLE 3)

As can be observed from table 3, a reduction in cerebral blood flow may be present with a

normal, increased, or decreased cerebral oxygen consumption, and may even occur in the presence of a decrease in cerebral vascular resistance. The inconsistency of the relationship among these various cerebral metabolic values lends credence to the belief that the rate of cerebral metabolism does not consistently influence cerebral vascular tone. There is little doubt that it plays a role in certain conditions, such as pernicious anemia and myxedema, but the mechanisms whereby changes in cerebral metabolism may influence cerebral vessel tone remain obscure.

Hyperventilation and Administration of 85 to 100 per cent Oxygen. The reduction of cerebral blood flow in hyperventilation seems to be related to the alkalosis resulting from the overbreathing, again adding support to the belief that hydrogen ion concentration is an important factor in the regulation of cerebral circulation, blood flow decreasing as blood pH rises.[49] The reason for the increased cerebral metabolism accompanying hyperventilation is not at all clear, particularly since such subjects usually show considerable depression in their level of awareness. The cerebral vascular constriction which accompanies the breathing of high oxygen content gas has been previously mentioned.

Polycythemia. The role of blood viscosity in cerebral circulation is exemplified by the increased vascular resistance accompanying polycythemia.[50] The thicker blood apparently offers greater frictional resistance to its flow through small vessels, and clinical confirmation of this phenomenon is seen in numerous cerebral symptoms, such as vertigo, giddiness, headache, and vascular occlusions, which accompany this disease.

Motionless Standing. Although an increase in the arterial pressure head does not result in increased cerebral blood flow, a great decrease in cerebral arterial pressure is usually followed by a reduction in blood flow, as indicated by data collected in normal subjects in the upright posture.[14] Under most circumstances the decreasing cerebral blood flow is compensated for by increased oxygen extraction by the brain so that cerebral metabolism remains normal. If this compensating mechanism is stretched too far, however, cerebral metabolism will probably fall and the subject will faint. This ability of the brain to maintain a stable rate of oxygen utilization during changes in blood flow when cellular function remains intact is also exemplified in heart failure, many patients with cerebral vascular disease, and following intravenous administration of aminophylline or caffeine. The fall in cerebral vascular resistance in the upright posture may represent true dilation of cerebral vessels in response to a drop in arterial pressure, or it may be the result of a decrease in pressure on the venous side of the capillaries, thereby decreasing peripheral resistance. Recent investigations on the human centrifuge indicate that a fall in cerebral arterial pressure induced by gravitational stress may be compensated for by strikingly decreased cerebral venous pressure with fairly adequate maintenance of cerebral circulation.[51]

TABLE 3.—*Group III. Cerebral Blood Flow Decreased*

	$CMRO_2$	CVR
Hyperventilation	Increased	Increased
O_2 (85–100%)	Normal	Increased
Polycythemia	Normal	Increased
Motionless Standing	Normal	Decreased
Increased Intracranial Pressure	Decreased	Increased
Cerebral Vascular Disease	Normal or Decreased	Increased
Heart Failure	Decreased	Increased
Aminophylline	Normal	Increased
Caffeine	Normal	Increased
Myxedema	Decreased	Increased
Pernicious Anemia	Decreased	Increased
Diabetic Acidosis	Decreased	Increased
Pentothal Narcosis	Decreased	Increased
Neurosyphilis	Decreased	Increased
ACTH or Cortisone	Decreased	Increased

Increased Intracranial Pressure. An increase in intracranial pressure results in an increase in cerebral vascular resistance, probably due to compression of cerebral vessels. Cerebral blood flow does not decrease, however, until intracranial pressure is three to four times its normal level, because the rising arterial pressure which accompanies a rising intracranial pressure partially compensates for the increased resistance.[52] This compensatory mechanism soon

fails, however, and cerebral hypoxia results in mental cloudiness and coma. The intimate communication of the cerebrospinal fluid with the veins of the body plays an important role in protecting the cerebral vessels from rapid changes in arterial or venous pressure (as in a sneeze or cough), for the increased pressure is immediately transmitted to the cerebrospinal fluid, thereby cushioning the cerebral vessels.

Cerebral Vascular Disease. Organic occlusion of cerebral vessels results in a progressive reduction in cerebral blood flow, which is at first compensated by increased oxygen extraction so that oxygen consumption remains normal despite a greatly increased cerebral vascular resistance.[32] As the occlusive disease progresses, however, the decreased blood flow can no longer be compensated by widening of the cerebral arteriovenous oxygen difference and cerebral oxygen consumption falls. There is a striking correlation in these patients between oxygen consumption and mental status and these studies demonstrate the various stages in the progression of cerebral vascular disease. In the presence of an already decreased cerebral blood flow the occurrence of any unusual drop in arterial pressure or momentary decrease in cardiac output may be sufficient to result in cerebral circulatory stasis and thrombosis. This may be the explanation for certain types of cerebral vascular accidents. The nitrous oxide procedure may also be used clinically to distinguish between certain types of affective and organic psychoses, for, as already mentioned, schizophrenic patients show no alteration in cerebral blood flow or metabolism.

Heart Failure. Although cerebral blood flow is reduced some 40 per cent below normal in chronic low output heart failure, greatly increased cerebral oxygen extraction results in only a small (13 per cent) decrease in cerebral oxygen consumption.[53] The mechanism for the increased cerebral vascular tone in heart failure is not yet known, but apparently the brain, like the liver, continues to receive its normal percentage share of the decreased cardiac output. The finding that cerebral blood flow and oxygen consumption are reduced in heart failure comes as somewhat of a surprise, for it has been felt that the disproportionate reduction in renal blood flow seen in heart failure was the result of the body's efforts to maintain a normal circulation in other organs. If such favored organs exist, the brain is not one of them. The great reduction in cerebral blood flow in heart failure is a physiologic explanation for the mental symptoms frequently seen in cardiac patients.

Aminophylline and Caffeine. The administration of aminophylline or caffeine apparently results in cerebral vascular constriction, even though normal cerebral metabolism is maintained.[37, 54] The use of such a drug in the treatment of cerebral vascular disease is obviously contraindicated.

The importance of local tissue needs as a regulator of cerebral blood flow and vascular resistance is demonstrated in the group of conditions in which the reduction of cerebral metabolism may be the mechanism which initiates the changes in blood flow and vascular resistance.

Myxedema. In myxedema the reduction in cerebral metabolism and blood flow and increase in vascular resistance are reversible following thyroid therapy,[55] suggesting that replacement of this metabolic substance permits the return of normal cellular metabolism and thereby increases the demand of the tissue for blood. It also appears that the reduction in cardiac output in myxedema is the result of the decreased tissue demands for blood. The abnormal mental symptoms of patients with myxedema, and even the syndrome of myxedematous madness, are probably due to the decreased cerebral metabolism, for there is an adequate correlation between the severity of mental status changes and degree of reduction of cerebral oxygen and glucose metabolism in myxedema. A similar type of situation may obtain in pentothal narcosis, paresis, and partially in diabetic coma.

Pernicious Anemia. Studies in pernicious anemia have served to emphasize the point that this disease cannot be considered as a simple anemia in its effects upon the cardiovascular apparatus.[56] The patients studied fell into two groups, those with severe anemia and those with moderate or no anemia. In the first group, cerebral blood flow was increased and

cerebral vascular resistance decreased; in the second group, cerebral blood flow was decreased and vascular resistance increased. In both groups, cerebral oxygen and glucose consumption were decreased. There was a good correlation between the mental status defects and cerebral oxygen consumption. Specific therapy (with liver or B_{12}) resulted in a moderate increase in cerebral oxygen consumption and cerebral vascular resistance. In no instance did cerebral oxygen consumption become normal, despite the fact that many of the patients returned to normal clinically. The patients with pernicious anemia demonstrate the unusual disparity which may occur between mental status and physical activity on the one hand and cerebral oxygen consumption on the other, for many of them were able to remain ambulatory and active with greatly decreased rates of oxygen and glucose metabolism. The studies also demonstrated that pernicious anemia results in specific nervous system involvement not related to the anemia and that this damage is at least partly irreversible. The results emphasize the great importance of early and accurate diagnosis in pernicious anemia so that therapy can be instituted before irreversible changes occur.

Diabetic Acidosis. The reduction in cerebral oxygen consumption in diabetic acidosis may be partially attributable to a fundamental derangement in the cellular biochemical processes responsible for the normal utilization of oxygen, but the presence of large quantities of circulating ketone bodies in diabetic acidosis also probably plays an important role in the reduction of cerebral metabolism. Early in diabetic acidosis there is a fair correlation between cerebral oxygen consumption and cerebral blood flow, but as acidosis progresses the decreasing blood pH produces a high cerebral blood flow and low cerebral vascular resistance even in the face of a strikingly decreased cerebral oxygen consumption.[45]

Pentothal Narcosis and Central Nervous System Syphilis. In Pentothal narcosis the primary mechanism responsible for the defects in cerebral metabolism and accompanying alterations of mental status and consciousness appears to be impaired cerebral cellular metabolic activity.[57] This depressant effect upon the brain cells in Pentothal narcosis is acute, usually temporary, and unquestionably due to the drug itself; the precise way in which it interferes with cellular metabolism is unknown. Studies on patients with meningovascular syphilis and paresis indicate that at least two mechanisms may be responsible for the measured reduction in cerebral metabolism and for the changes in mental status which may occur in these conditions.[58] Small vessel occlusion as a result of the syphilis may cause cerebral ischemia and reduction in cerebral blood flow and metabolism. The reduction in cerebral metabolism may also be due mainly to primary injury of the brain cells by the disease, rendering them incapable of utilizing oxygen properly, and resulting in diminished cerebral blood flow secondarily. The increase in cerebral blood flow and metabolism following specific therapy (fever and penicillin) supports, at least partially, this latter hypothesis.

In all these conditions cerebral vascular tone and cerebral blood flow appear to be regulated, in part, by cerebral metabolic demands. A reduction in cerebral metabolism, whether it is the result of a lack of an indispensible cellular metabolite or the presence of an injurious foreign agent, is apparently capable of stimulating an increased cerebral vascular resistance and decreased blood flow. That this is not inevitably true is demonstrated by the greatly reduced cerebral vascular resistance which may accompany a low cerebral metabolism in insulin shock or some phases of diabetic acidosis, and the normal cerebral vascular resistance which accompanies decreased cerebral metabolism in uremia. Even so, the importance of local tissue needs as a regulator of cerebral blood flow cannot be dismissed. The mechanisms whereby decreased cellular metabolism results in these changes have not yet been elucidated.

Adrenocorticotropic Hormone (ACTH) and Cortisone. The administration of ACTH and cortisone results in a reduction in cerebral blood flow and cerebral metabolism and increased vascular resistance, findings which may explain the alterations in mental status frequently noted in patients being treated with these preparations. The mechanisms for these altera-

tions in cerebral metabolic functions are not clear; the metabolic alkalosis accompanying ACTH or cortisone administration may be partially responsible.[59]

In summary, it can be stated that the regulation of cerebral blood flow and metabolism is accomplished by a variety of complex mechanisms, all of which appear to operate interdependently. These factors include the arterial pressure head, blood viscosity, cerebral venous tone, intracranial pressure, degree of cerebral vascular occlusion, blood pH, blood oxygen and carbon dioxide content, and local cerebral tissue requirements. By investigating these mechanisms, we have enhanced our knowledge of many diseases affecting the brain and thereby are able to approach their therapy more rationally. Changes in mental status, if characterized by an alteration in the level of awareness of the patient, are usually accompanied by a decrease in cerebral metabolism; however, changes in mental function and great alterations in behavior pattern of a patient, such as in schizophrenia, are not necessarily related to abnormal cerebral metabolism. The causes for this type of mental aberration remain to be discovered. The great potentialities of any investigative procedure which permits inquiry into the intricacies of mental function are obvious, as is the eventual value of these investigations to the clinical physician in his handling of patients.

REFERENCES

[1] KETY, S. S., AND SCHMIDT, C. F.: The determina- of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am. J. Physiol. **53:** 143, 1945.

[2] GREGG, D. E., AND SHIPLEY, R. E.: Experimental approaches to the study of the cerebral circulation. Federation Proc. **3:** 144, 1944.

[3] FLOREY, N.: Microscopical observations on the circulation of blood in the cerebral cortex. Brain **48:** 43, 1928.

[4] FORBES, H. S., AND WOLFF, H. G.: Cerebral circulation. III. The vasomotor control of cerebral vessels. Arch. Neurol. & Psychiat. **19:** 1057, 1928.

[5] WOLFF, H. G., AND LENNOX, W. G.: Cerebral circulation. XII. The effect on pial vessels of variations in the O_2 and CO_2 content of the blood. Arch. Neurol. & Psychiat. **23:** 1097, 1930.

[6] FINESINGER, J. E.: Cerebral circulation. XVIII. Effect of caffeine on the cerebral vessels. Arch. Neurol. & Psychiat. **28:** 1290, 1932.

[7] LENNOX, W. G., AND GIBBS, E. L.: Blood flow in brain and leg of man, and the changes induced by alterations in blood gases. J. Clin. Investigation **11:** 1155, 1932.

[8] —: Constancy of the cerebral blood flow. Arch. Neurol. & Psychiat. **36:** 375, 1936.

[9] GIBBS, F. A., MAXWELL, H., AND GIBBS, E. L.: Volume flow of blood through the human brain. Arch. Neurol. & Psychiat. **57:** 137, 1947.

[10] FERRIS, E. B., JR.: Objective measurement of relative intracranial blood flow in man, with observations concerning the hemodynamics of the craniovertebral system. Arch. Neurol. & Psychiat. **46:** 377, 1941.

[11] SCHEINBERG, P.: Simultaneous bilateral determinations of cerebral blood flow and arterial-cerebral venous oxygen and glucose differences. Proc. Soc. Exper. Biol. & Med. **74:** 575, 1950.

[12] WECHSLER, R. L., DRIPPS, R. D., AND KETY, S. S.: Blood flow and oxygen consumption of the human brain during anesthesia produced by thiopental. Anesthesiology **12:** 308, 1951.

[13] KETY, S. S., AND SCHMIDT, C. F.: The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. J. Clin. Investigation **27:** 476, 1948.

[14] SCHEINBERG, P., AND STEAD, E. A., JR.: The cerebral blood flow in male subjects as measured by the nitrous oxide technique. Normal values for blood flow, oxygen utilization, glucose utilization and peripheral resistance, with observations on the effect of tilting and anxiety. J. Clin. Investigation **28:** 1163, 1949.

[15] MYERS, J. D.: Net splanchnic glucose production in normal man and in various disease states. J. Clin. Investigation **29:** 1421, 1950.

[16] GIBBS, E. L., LENNOX, W. G., NIMS, L. F., AND GIBBS, F. A.: Arterial and cerebral venous blood, arterial-venous differences in man. J. Biol. Chem. **144:** 325, 1942.

[17] HIMWICH, W. A., AND HIMWICH, H. E.: Pyruvic acid exchange of the brain. J. Neurophysiol. **9:** 133, 1946.

[18] ROSSEN, R., KABAT, H., AND ANDERSON, J. P.: Acute arrest of the cerebral circulation in man. Arch. Neurol. & Psychiat. **50:** 510, 1943.

[19] SHENKIN, H. A., HARMEL, M. H., AND KETY, S. S.: Dynamic anatomy of the cerebral circulation. Arch. Neurol. & Psychiat. **60:** 240, 1948.

[20] SHENKIN, H. A., CABIESES, F., VAN DEN NOORDT, G., SAYERS, P., AND COPPERMAN, R.: The hemodynamic effect of unilateral carotid ligation on cerebral circulation of man. J. Neurosurg. **8:** 38, 1951.

[21] HICKAM, J. B., CARGILL, W. H., AND GOLDEN, A.: Cardiovascular reactions to emotional stimuli; effect on the cardiac output, arteriovenous oxy-

gen difference, arterial pressure and peripheral resistance. J. Clin. Investigation **27:** 290, 1948.

[22] Myers, J. D., Brannon, E. S., and Holland, B. C.: A correlative study of the cardiac output and the hepatic circulation in hyperthyroidism. J. Clin. Investigation **29:** 1069, 1950.

[23] Scheinberg, P.: Cerebral circulation and metabolism in hyperthyroidism. J. Clin. Investigation **29:** 1010, 1950.

[24] Altschule, M. D., Freedberg, A. S., and McManus, M. J.: Circulation and respiration during episode of chill and fever in man. J. Clin. Investigation **24:** 878, 1945.

[25] Heyman, A., Patterson, J. L., Jr., and Nichols, F. T., Jr.: The effects of induced fever on cerebral functions in neurosyphilis. J. Clin. Investigation **29:** 1335, 1950.

[26] Kety, S. S.: Personal communication.

[27] —, Hafkenschiel, J. H., Jeffers, W. A., Leopold, I. H., and Shenkin, H. A.: The blood flow, vascular resistance and oxygen consumption of the brain in essential hypertension. J. Clin. Investigation **27:** 511, 1948.

[28] Hafkenschiel, J. H., Crumptom, C. W., Shenkin, H. A., Mayer, J. H., Zintel, H. A., Wendel, H., and Jeffers, W. A.: The effects of twenty degree head-up tilt upon the cerebral circulation of patients with arterial hypertension before and after sympathectomy. J. Clin. Investigation **30:** 793, 1951.

[29] Kety, S. S., King, B. D., Horvath, S. M., Jeffers, W. A., and Hafkenschiel, J. H.: The effects of an acute reduction in blood pressure by means of differential spinal sympathetic block on the cerebral circulation of hypertensive patients. J. Clin. Investigation **29:** 402, 1950.

[30] Hafkenschiel, J. H., Crumpton, C. W., Mayer, J. H., and Jeffers, W. A.: The effects of dihydroergocornine on the cerebral circulation of patients with essential hypertension. J. Clin. Investigation **29:** 408, 1950.

[31] Shenkin, H. A., Hafkenschiel, J. H., and Kety, S. S.: Effects of sympathectomy on the cerebral circulation of hypertensive patients. Arch. Surg. **61:** 319, 1950.

[32] Scheinberg, P.: Cerebral blood flow in vascular disease of the brain with observations on the effects of stellate ganglion block. Am. J. Med. **8:** 139, 1950.

[33] Harmel, M. H., Hafkenschiel, J. H., Austin, G. M., Crumpton, C. W., and Kety, S. S.: The effect of bilateral stellate ganglion block on the cerebral circulation in normotensive and hypertensive patients. J. Clin. Investigation **28:** 415, 1949.

[34] Shenkin, H. A., Cabieses, F., and van den Noordt, G.: The effect of bilateral stellectomy upon the cerebral circulation of man. J. Clin. Investigation **30:** 90, 1951.

[35] Scheinberg, P. The effect of nicotinic acid on the cerebral circulation with observations on extracerebral contamination of cerebral venous blood in the nitrous oxide procedure for cerebral blood flow. Circulation **1:** 1148, 1950.

[36] Scheinberg, P., Jayne, H. W., Rich, M., and Belle, M. S.: The effects of intravenous papaverine and procaine on cerebral circulation and metabolism. J. Clin. Investigation **30:** 671, 1951.

[37] Shenkin, H. A.: Effects of various drugs upon cerebral circulation and metabolism in man. J. Applied Physiol. **3:** 465, 1951.

[38] Kety, S. S., Woodford, R. B., Harmel, M. H., Freyhan, F. A., Appel, K. E., and Schmidt, C. F.: Cerebral blood flow and metabolism in schizophrenia. Am. J. Psychiat. **104:** 765, 1948.

[39] Kety, S. S., Lukens, F. D. W., Woodford, R. B., Harmel, M. H., Freyhan, F. A., and Schmidt, C. F.: The effect of insulin hypoglycemia and coma on human cerebral metabolism and blood flow. Federation Proc. **7:** 64, 1948.

[40] Heyman, A., Patterson, J. L., Jr., and Jones, R. W., Jr.: Cerebral circulation and metabolism in uremia. Circulation **3:** 558, 1951.

[41] Bentinck, R. C., Gordon, G. S., Adams, J. E., Arnstein, L. H., and Leake, T. B.: Effect of desoxycorticosterone glucoside upon cerebral blood flow and metabolism of human subjects. J. Clin. Investigation **30:** 200, 1951.

[42] McCall, M. L.: Cerebral blood flow and metabolism in toxemias of pregnancy. Surg., Gynec. & Obst. **89:** 715, 1949.

[43] Shenkin, H. A., Scheuerman, W. G., Spitz, C. B., and Graff, R. A.: The effects of change of position upon the cerebral circulation of man. Am. J. M. Sc. **216:** 714, 1948.

[44] Kety, S. S., and Schmidt, C. F.: Effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J. Clin. Investigation **27:** 484, 1948.

[45] Kety, S. S., Polis, B. D., Nadler, C. S., and Schmidt, C. F.: The blood flow and oxygen consumption of the human brain in diabetic acidosis and coma. J. Clin. Investigation **27:** 500, 1948.

[46] Scheinberg, P.: Unpublished data.

[47] Shenkin, H. A., Spitz, E. B., Grant, F. C., and Kety, S. S.: Physiological studies on arteriovenous anomalies of the brain. J. Neurosurg. **5:** 165, 1948.

[48] Mangold, R., Sokoloff, L., Therman, P. O., Conner, E. H., Kleinerman, J. S., and Kety, S. S.: Cerebral blood flow and oxygen consumption during natural sleep. Federation Proc. **10:** 89, 1951.

[49] Kety, S. S., and Schmidt, C. F.: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, car-

diac output and blood pressure of normal young men. J. Clin. Investigation **25:** 107, 1946.

[50] —: Circulation and metabolism of the human brain in health and disease. Am. J. Med. **8:** 205, 1950.

[51] HENRY, J. P., GAUER, O. H., KETY, S. S., AND KRAMER, K.: Factors maintaining cerebral circulation during gravitational stress. J. Clin. Investigation **30:** 292, 1951.

[52] KETY, S. S., SHENKIN, H. A., AND SCHMIDT, C. F.: The effects of increased intracranial pressure on cerebral circulatory functions in man. J. Clin. Investigation **27:** 493, 1948.

[53] SCHEINBERG, P.: Cerebral circulation in heart failure. Am. J. Med. **8:** 148, 1950.

[54] WECHSLER, R. L., KLEISS, L. M., AND KETY, S. S.: The effects of intravenously administered aminophylline on cerebral circulation and metabolism in man. J. Clin. Investigation **29:** 28, 1950.

[55] SCHEINBERG, P., STEAD, E. A., JR., BRANNON, E. S., AND WARREN, J. V.: Correlative observations on cerebral metabolism and cardiac output in myxedema. J. Clin. Investigation **29:** 1139, 1950.

[56] SCHEINBERG, P.: Cerebral blood flow and metabolism in pernicious anemia. Blood **6:** 213, 1951.

[57] HIMWICH, W. A., HOMBURGER, E., MARESCA, R., AND HIMWICH, H. E.: Brain metabolism in man: unanesthetized and in pentothal narcosis. Am. J. Psychiat. **103:** 689, 1947.

[58] PATTERSON, J. L., JR., HEYMAN, A., AND NICHOLS, F. T., JR.: Cerebral blood flow and oxygen consumption in neurosyphilis. J. Clin. Investigation **29:** 1327, 1950.

[59] SCHIEVE, J. F., SCHEINBERG, P., AND WILSON, W. P.: The effects of adrenocorticotrophic hormone (ACTH) on cerebral blood flow and metabolism. J. Clin. Investigation **30:** 671, 1951.

The Spatial Vectorcardiogram Obtained by Use of a Trihedron and Its Scalar Comparisons

By PIERRE W. DUCHOSAL, M.D., AND JEAN R. GROSGURIN, M.D.

The spatial vectorcardiogram is supposed to represent the path of the cardiac vector viewed from a rather large distance. With this in mind, the authors propose a vectorcardiographic method based on a trirectangular trihedron. Comparisons are made between calculated scalar leads derived from the spatial vectorcardiogram, and real scalar leads recorded from the subject. In case of concordance the hypothesis of a single instantaneous cardiac vector within an homogeneous conducting medium is verified. This was found to hold for most circumstances. However, for those instances in which discrepancies arose another hypothesis is advanced.

SPATIAL vectorcardiography intends to represent the variations of the instantaneous cardiac vector as a function of time. This generally accepted definition implies the idea of an instantaneous resultant of all the elementary electrical sources of the heart. In principle such a resultant can be conceived or represented only if all electrical sources are viewed from a rather great distance, bearing in mind the volume occupied by the generator organ, the heart. Admitting that the vectorcardiogram which expresses the successive resultants can be obtained, the actual problem consists in knowing to what extent the successive fields corresponding to these resultants agree with the real electrical fields of the heart, as they are accessible on the human body in the form of multiple scalar tracings recorded at various points on the surface or even from the interior of the human body.

In the attempt to resolve this problem, we started with the spatial vectorcardiographic tracing taken at a given distance from the heart and used a method of leading based on a trirectangular trihedron.[1, 2] The latter is different from the trihedron previously proposed by Schellong.[3] The actual research consisted in comparing [2, 4–6] the scalar electrocardiograms derived from this vectorcardiogram and the real scalar electrocardiograms.

This study necessitates certain remarks concerning the conducting medium of the body. Several opinions have been voiced on this subject of which two have claimed our attention, that of Wilson, on the one hand, and that of Burger on the other.

Wilson,[7–9] like Einthoven, accepted the simplified representation of instantaneous electrical cardiac sources in the form of a single dipole placed centrally or eccentrically within a sphere of homogeneous conductibility. He considered that this simplification took into account a certain number of observed facts with sufficient accuracy to explain the principles governing the distribution of potentials within the body. Nonetheless, Wilson, having also considered the fact that these sources occupy an important volume, has been led recently[10] to resort to the use of the physical expression of Poisson's integral. The latter gives a better approximation to the reality than does the first concept which considered only a single dipole. The two conceptions are not, however, in opposition to one another.

More recently Burger,[11] considering the irregularity and heterogeneity of the human body as a conductor, tried to avoid comparisons with an homogeneous medium, spherical or not spherical. The composition and form of the body's conductors being unknown, Burger tried to imitate the actual conditions by using a mannequin. Inside this "phantom" he placed an artificial dipole in several places within the region occupied by the heart. In doing this, he

From the Department of Cardiology, first medical service, Hôpital Cantonal, Geneva, Switzerland.

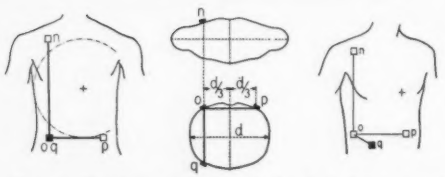


FIG. 1. Bipolar vectorgraphic leads defining a right trihedral angle, as used by the authors. The four lead points *n o p q* are equidistant from the center of the heart, represented here by a cross. In the perspective view (to the right) the points *n o p*, pictured as empty squares, lie in the plane of the back. In the center, section of the trunk at level *n* and *o*; *d* = transverse diameter of the body at the level *o*.

likewise considered the hypothesis of an instantaneous electrical resultant. This process permitted him to demonstrate experimentally the distribution of the potentials, that is, the electrical field produced at all points of the phantom, and at the same time led him to a logical and individual method of recording a human vectorcardiogram.[12]

METHOD

In our research, we have chosen the most accessible hypothesis for a comparative method, that which supposes an homogeneous body medium containing at every instant a single resultant dipole or vector.

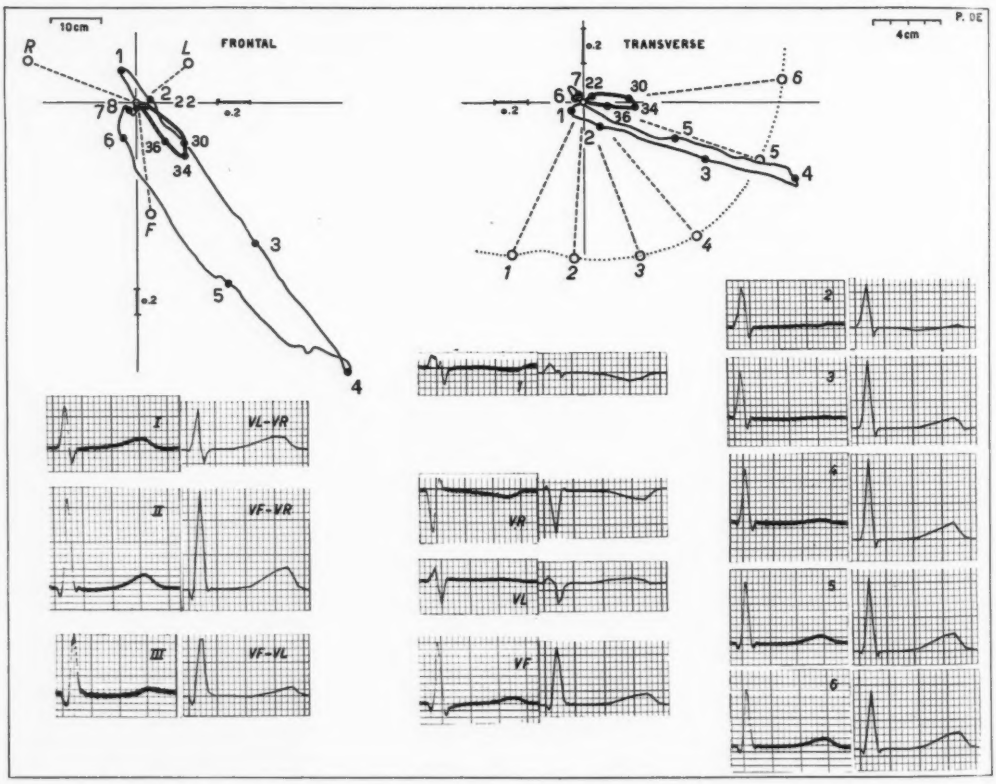


FIG. 2. Normal subject, 22 years old. *Above:* frontal and transverse vectorcardiogram (accurate copies of original tracings). The numbers corresponding to points along the vectorcardiogram indicate the time in hundredths of a second. The T curve is drawn in more darkly than QRS. The P curve is not represented. The scale of amplification of the vectorgraphic curves is indicated on perpendicular axes of the vectorcardiograph figures (0.2 millivolt). The broken lines represent the actual unipolar axes V_R, V_L, V_F and V_1 to V_6 (slanted numbers) made from precise measurements on the subject. (See corresponding scales in centimeters.) The dotted lines connecting points 1 to 6 (that is, V_1 to V_6) reproduce part of the transverse perimeter of the thorax, obtained by molds, at the level of the center of the ventricular mass. *Below:* Table of comparisons between real electrocardiogram, to the left in each of three columns, and the electrocardiogram derived from the vectorcardiogram, to the right in each of three columns. Time = 0.02 second.

We have also considered the hypothesis of several components, that is, synchronous dipoles which cannot be replaced by a single dipole in certain definite cases. The conditions of a sphere or infinite volume have permitted recourse to simple physical formulas in both circumstances. In the case of the hypothesis of a single instantaneous resultant, sometimes a point with a fixed origin and common to successive vectors was considered; at other times, a point of origin moving as a function of the time.

moment, requires comment. The trirectangular trihedron used to register the spatial vectorcardiogram taken at a given distance is defined by four points of application on the body as shown in figure 1. The choice of these four points, cited in a previous contribution,[2] is defined by their equidistance from the ventricular mass. They determine three lines of bipolar orthogonal leads whose lengths are most often unequal. This last fact necessitates, in compliance with the theory, corrections of amplification as im-

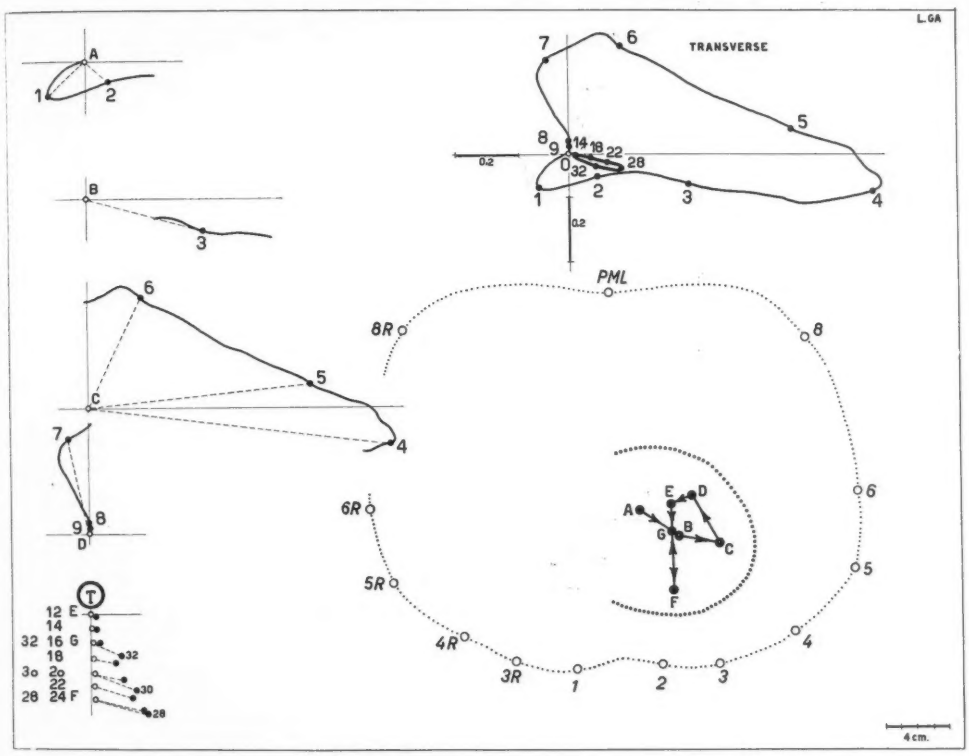


FIG. 3. Normal subject, 29 years old. *Right upper:* transverse vectorcardiogram. *Right lower:* thoracic perimeter with unipolar lead points; interior, anatomic contour of the ventricular mass as delimited by radiologic control. Inside the heart, points $A, B, \ldots G$ designate the successive positions of the point of origin of the vectors during QRS-T. These letters correspond to precise instants of the vectorcardiogram shown separately to the *left* of the figure. The broken lines used here indicate the vector radii. For other notations and markings, see figure 2.

The comparative method mentioned above is based on the electrical moments of the successive resultant dipoles expressed by the vectors of the spatial vectorcardiogram. From these vectors the presumed potentials are calculated for any given point on the surface or inside the body. The results expressed in the form of scalar quantities varying with the time are compared with the true electrocardiograms registered at these same points.[2, 6]

The basic determination, that of the electrical

posed by the known formulas.[6, 13] These corrections have been applied in this present work.

Under these conditions the vectorcardiogram permits the calculations of the electrical moments of successive cardiac dipoles, the various distances being accessible.[2, 6]

Starting with a spatial vectorcardiogram made according to this principle, it is easy to deduce all scalar leads, unipolar or bipolar. Three factors must be taken into account: (1) the cardiac vector in

space, (2) the axis of the chosen lead, and (3) the distance to the center of the heart.

In comparing the calculated tracing with the real tracing taken at a given point, account is taken of the timing and the voltage of the two scalar tracings, real and calculated. The comparisons so made consider, in the main, points situated in the frontal plane of the body and in a transverse plane passing through the center of the heart. Those points concerning the frontal plane are V_R, V_L, V_F, and consequently the standard leads. For the case of the transverse plane, we have transposed the positions of the points V_1 to V_8 as well as those from V_{3R} to V_{8R} and the medial posterior line (MPL) to the same transverse plane passing through the fifth or at times the sixth intercostal, parasternal space. The level (fifth or sixth space) is selected in each particular case according to the localization of the anatomic center of gravity of the ventricles as determined by radiologic methods, the subject lying in the supine position. This alignment of the precordial points is not exactly in conformity with standardized conventions which place the points of application V_1 to V_6 along a broken line. The nonobservance of these conventions avoids additional work which in the long run would render little profit to the proposed research.

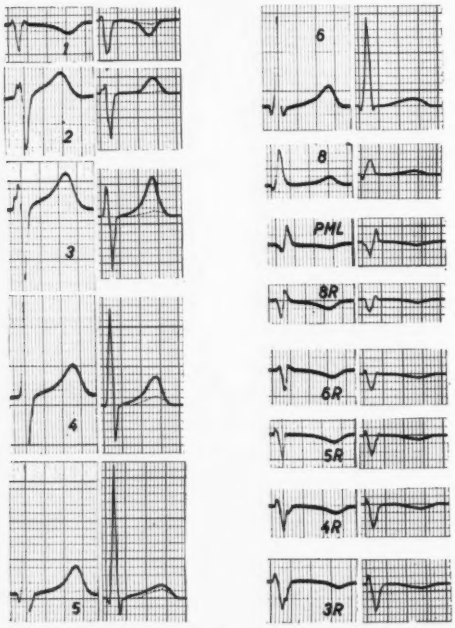


FIG. 4. Same patient shown in figure 3. Comparison of scalar tracing. The electrocardiograms labeled *1, 2, . . . 3R* (i.e. V_1 V_2 . . . V_{3R}) are the real recorded tracings. The calculated tracings are placed beside the latter. The dotted T waves on electrocardiograms *1, 2, 3, 4, 5*, are drawn from calculations assuming a fixed origin for all T vectors (on point *E* of fig. 3).

The few comparisons which are made for leads from the interior of the body are drawn from a series of unipolar axes which are not necessarily placed in a single plane. Therefore the derived scalar leads were drawn from plastic models of the spatial vectorcardiograms.

In all these circumstances the location of all lead points of the actual electrocardiograms has been determined as accurately as possible. Individual body measurements and thoracic molds[2, 6] were utilized and we were also guided by radiographs taken in two orthogonal planes. Our vectorcardiographic recorder is a three channel amplifier with double beam cathode ray tube.

MATERIAL AND RESULTS

The spatial vectorcardiograms of 102 subjects have been compared with the scalar electrocardiograms according to the principles indicated above. The hypothesis of a resultant vector whose point of origin is either fixed or mobile has been verified for 94 subjects: 31 normal subjects, nine patients with left ventricular hypertrophy, two with right ventricular hypertrophy, seven with left and eight with right bundle branch block, 17 with myocardial infarction, six with the Wolff-Parkinson-White syndrome, 13 with congenital anomalies, and one with a Lutembacher syndrome. The hypothesis of a resultant vector has not been found adequate for eight subjects: four patients with mitral stenosis, one with right ventricular hypertrophy, one with cor triloculare, one with the Lutembacher syndrome and one with myocardial infarction. Six representative cases are discussed in detail in the next paragraphs.

(1) *Example of a Case in Which the Hypothesis of a Fixed Point of Origin of the Resultant Vectors is Verified*

The case is that of a normal male, 22 years old, of a pyknic build. The point of origin common to the vectors during QRS-T is placed at the anatomic center of gravity of the ventricles (the center was located radiographically). Figure 2 shows the frontal and horizontal vectorcardiogram and the real unipolar axes of leads V_R, V_L, V_F, as well as V_1 to V_6. Considering the unequal distances of V_R, V_L and V_F from the cardiac center, the values for the standard leads I, II and III are obtained by arithmetic subtraction from the unipolar values, i.e. $V_L - V_R$, $V_F - V_R$, $V_F - V_L$, and not by simple projections on the lines of the bipolar leads L_R, R_F and L_F. The

results of the comparison of these 12 leads are shown by the tracings placed in the lower part of the figure. The approximation that was obtained has been judged good enough to suggest that the proposed hypothesis is verified.

points of origin at different instants of QRS-T. Thus, knowing the length of the thoracic diameter and the potentials existing at each of the two extremities, we have calculated the position of the point of origin of the cardiac vector on this axis. The letters *A*, *B*,

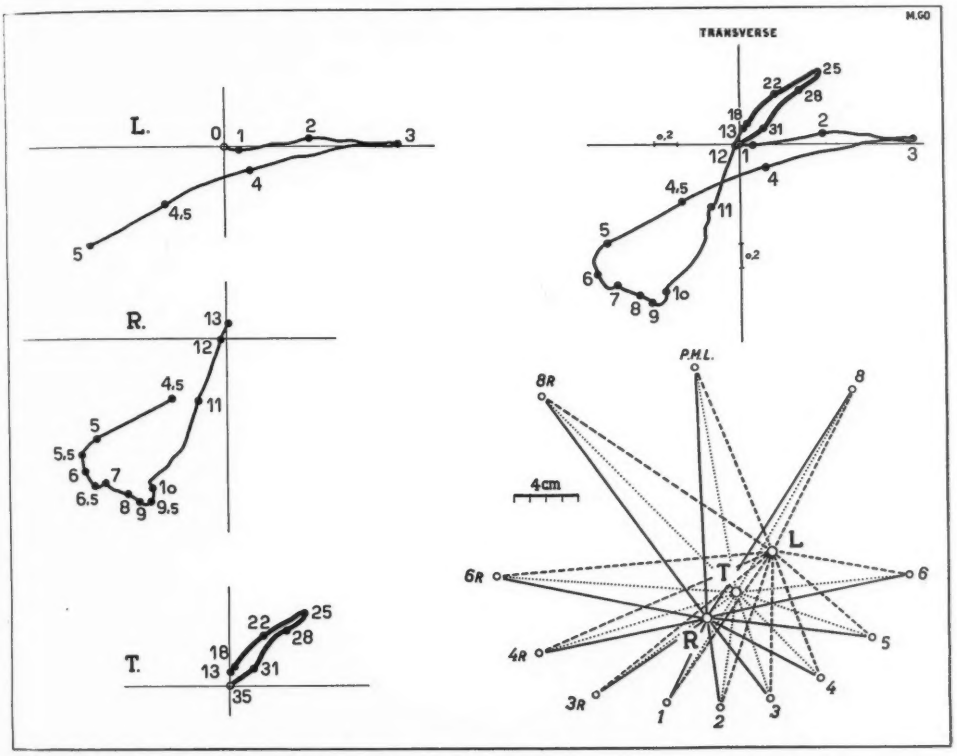


FIG. 5. Right bundle branch block. Female, 55 years of age. Pulmonary sclerosis plus mitral stenosis. *Right upper:* transverse vectorcardiogram. Same explanatory notations as in figure 3. *Right lower:* locations of electrodes around the thorax. Letters *LRT* designate the origin of the resultant cardiac vectors at three distinct instants of QRS-T cycle. *L* and *R* represent respectively the successive left and right origins of the vectors and happen to correspond to the anatomic territories of the left and right ventricles. *T* is the common point of origin for all *T* vectors for both ventricles. The radii emanating from *L*, *R* and *T* trace the axes of all the unipolar leads. On the *left*, the vectorcardiographic loop is broken up into three pieces corresponding to the three instants *L*,*R*,*T* of the cycle.

(2) *Example of a Case in Which the Hypothesis of a Continuous Displacement of the Point of Origin of Successive Vectors during QRS-T is Verified*

The case serving for this illustration is again that of a normal male, aged 29, 180 cm. tall, of an athletic build. Figure 3 shows his transverse vectorcardiogram which alone is discussed. The comparisons of 13 unipolar leads taken at the periphery of a transverse plane at the level of the fifth intercostal space have served for the calculated determination of the ... *G* indicate the centers so determined. Each of them is valid for only a part of the vectors. It is shown that the displacement follows a certain path always within the anatomic limits of the heart. Note that *A* and *B* are located in the region of the septum; *C* and *D* are in the zone of the left ventricle; *E*, *F* and *G* (T wave) are on a straight line, confirming what we had found recently to be the case in other normal subjects.[14] Figure 4 gives the collected comparisons between the real scalar leads and scalar leads constructed on this principle. The conformity of the tracings with respect to chronol-

ogy and voltage has been deemed sufficient to claim that the hypothesis of a displacement of the point of origin is verified.

(3) *Example of a Case of Right Bundle Branch Block in Which the Hypothesis of Three Principal, Successive Points of Origin during QRS-T is Verified*

The successive stimulation of left and right territories brought about by a bundle branch block is a favorable condition for the study of two distinct

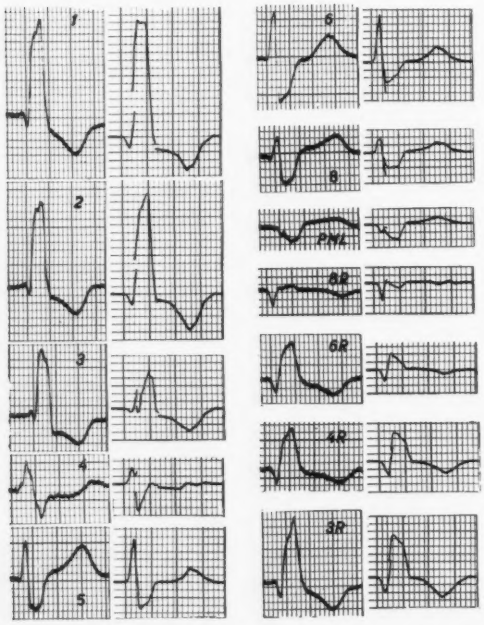


FIG. 6. Same patient shown in figure 5. Comparison of scalar tracings. The electrocardiograms labeled *1, 2, . . . 3R* (i.e., V_1 V_2 . . . V_{3R}) are the real recorded tracings; the corresponding calculated tracings are matched at the right of the recorded tracings.

points of origin of the cardiac vectors. As in the preceding case, the location of the points of origin has been worked out by calculation and comparison of the opposite leads all around the thorax on a transverse plane passing through the fifth intercostal space. The case chosen here is that of a 50 year old woman with pulmonary sclerosis and mitral stenosis. She presented marked right ventricular hypertrophy. The horizontal vectorcardiogram taken at the level of the waist according to the technic of the spatial vectorcardiogram is reproduced in figure 5. To the left of this same figure, the vectorcardiogram is broken up into three parts: the first part, *L*, going from 0 second to 0.05 second and corresponding in all probability to the electrical effects of the primary excitation of territories dependent upon the intact left branch; the second, *R*, going from 0.045 second to 0.13 second translates the effects of the remaining ventricular territories situated in the right part of the heart; the third, *T*, translates the effects of collective repolarization of the ventricles. Below and to the right of the same figure the positioning of the 13 thoracic leads and the place of the three points of origin of the vectors *L*, *R* and *T* are represented on a reduced scale. The unipolar axes going from *L*, *R* and *T* to the 13 points are shown clearly so that the reader can appreciate their direction and the distances. As in the preceding case, it is to be noted that the three centers are placed within the anatomic limits of the heart and that *R* and *L* correspond to the anatomic localizations of the right and left ventricles, *T* being between them.

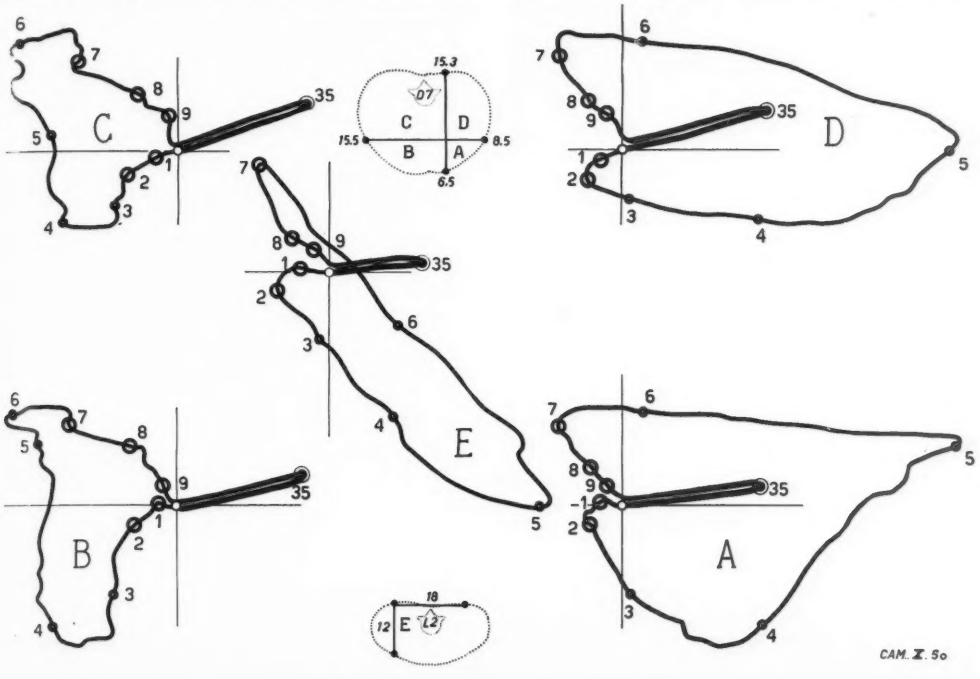
The scalar curves derived in this manner and the real scalar curves are shown in figure 6. Again good agreement between the two series of tracings can be seen, from the aspect of chronology as well as of the configuration of the various peaks. It is interesting to note that this excellent agreement is manifested equally for so-called semidirect leads such as V_1 and V_2, and for more distant leads, for instance V_{6R} and V_{8R}. A partial discordance exists between real and calculated curves for V_3 and V_4. As far as the general amplitude or voltage of the tracings is concerned, a good correspondence can be shown for the majority of the curves; the greatest difference to be observed is in V_{6R}.

In spite of these minor differences it is surprising to see the startling similarity of the two series of electrocardiograms. This fact should be emphasized in this example where the slenderness of the thorax and the great enlargement of the heart created conditions which resulted in the electrodes being very near the heart. For this reason we feel it can be said that the proposed hypothesis is upheld.

(4) *Example of a Case Where, for a Part of the Period of Depolarization Only, the Hypothesis of a Single Electrical Resultant Cannot be Upheld*

The case which serves to illustrate this example is characterized by conditions which are well known in scalar electrocardiography. These conditions are mitral stenosis accompanied by marked right ventricular hypertrophy. The patient was a 17 year old male. At first glance it can be seen that the opposite unipolar leads do not give mirror images. The study of this example has been done by a slightly different method than that applied heretofore, and consists in comparing four unipolar vectorcardiograms according to the four quadrants of a transverse plane at the level of the heart (fig. 7).

At the center of the four figures a fifth one is to be noted which is the horizontal vectorcardiogram taken at a given distance in the way described above for the registration of the spatial vectorcardiogram. The disagreement between the five figures seems to prove the nonvalidity of the hypothesis of a single resultant. Here the chronologic matching of the five vectorcardiograms calls for an immediate comment. The vectors 3, 4, 5 and 6 are in fact not comparable either in direction or in amplitude. On the other hand, the vectors 1, 2, 7, 8 and 9, that is to say the beginning and end of the rapid ventricular complex, as well as the whole of the T wave, are in agreement to a degree of approximation which meets with the conditions invoked in the first paragraph (fig. 2). The data confirm the validity of the hypothesis of an instantaneous resultant vector with a fixed point of origin for the greater



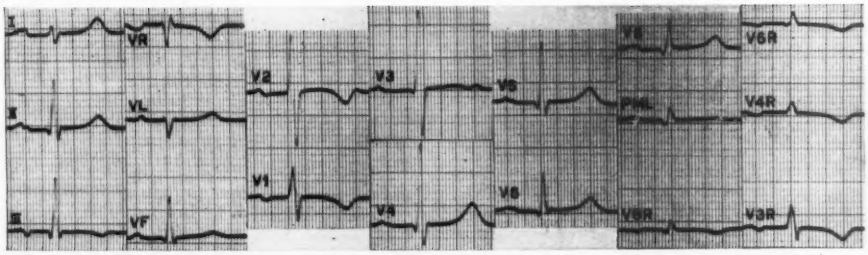


FIG. 7. Male, 17 years, mitral stenosis. *Above:* series of transverse vectorcardiograms. *A*,*B*,*C*,*D*, are combinations, two by two, of unipolar leads as indicated on the upper thoracic section. Amplification is adjusted for each of these four leads in direct proportion to the square of the lengths, as measured from the electrode to the center of the ventricles. Lengths are given in centimeters. Vectorcardiogram *E* is obtained from two bipolar leads at the inferior level of the trunk, using two leads of the trihedron. Lower section of trunk indicates the dimensions. T loop is drawn in more thickly than QRS. The points indicated by a circle along the five vectorcardiograms indicate the concordant vectors (see text). *Below:* recorded scalar leads.

part of QRS-T. But the complete discrepancy for a part of the vectors of QRS requires the following consideration: the hypothesis of an instantaneous

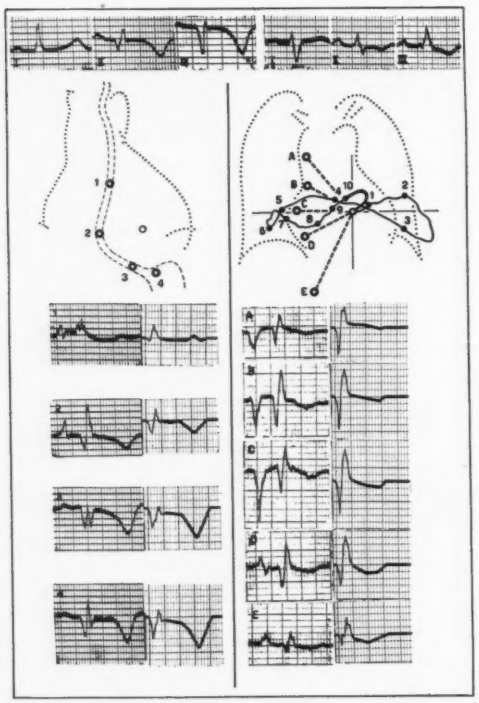


FIG. 8. Two examples of scalar comparisons concerning intrathoracic unipolar electrocardiogram. *On the left*, posterior myocardial infarction. Standard leads I, II, III, orthodiagram with esophagus and esophageal leads. Tracings 1, 2, 3, 4 correspond to the different sites of the esophageal electrode as indicated on the orthodiagram. *On the right*, chronic pulmonary disease with right ventricular hypertrophy and right bundle branch block. Standard leads I, II, III, orthodiagram with frontal vectorcardiogram and intravascular leads. Tracings *A*, *B*, . . . *E* correspond to the different sites of tip of intravascular catheter as indicated on the orthodiagram. The broken lines indicate the five unipolar axes emanating from the center of the ventricular mass; here this center is assumed to correspond to point of origin of the vectorcardiogram. In both columns of tracings the real electrocardiograms are labeled and placed on the left side; the corresponding calculated electrocardiograms are to the right.

resultant cannot be accepted, in spite of the effort made to find one or several adequate points of origin. An attempt to explain this phenomenon is given in the course of the discussion.

(5) *Example in Which Comparison of Unipolar Electrocardiograms Recorded inside the Trunk and Calculated Electrocardiograms Verifies the Hypothesis of a Fixed Point of Origin for the Vectors during QRS-T.*

The internal leads to be considered concern esophageal points and intravascular points in the venae cavae and the right atrium. The leads have been recorded by means of esophageal electrodes and venous catheterization in several cases of which two are given below as examples.

The first (fig. 8) concerns esophageal leads in a subject 58 years of age who had had a posterior infarction of the myocardium three years before. The calculated scalar tracings for comparison have been derived from a plastic model of the spatial vectorcardiogram because of the evident fact that points 1, 2, 3 and 4 define, with the center of the ventricles, unipolar axes that are not contained within one single plane.

The calculated scalar tracings are derived from vector projections on four axes of the same spatial direction as the real unipolar axes in the body. This difficult determination has been carried out by use of successive frontal and profile radioscopic determinations made for each new position of the esophageal electrode. The real tracings in the same positions are matched with the derived curves without accounting for the factor of absolute amplitude imposed by the different distances to the center of the heart. Therefore, the comparison is applicable only to the chronology and the configuration of the tracings. The agreement of the two series is satisfactory even though this case concerns a posterior myocardial infarction and esophageal tracings. Consequently we venture to claim that with this patient the hypothesis of an instantaneous resultant and of a fixed point of origin for all of the vectors is rather well maintained.

The second example (fig. 8) has been drawn from intravascular leads obtained by venous catheterization in a subject 55 years old suffering from a chronic pulmonary disease plus first degree right bundle branch block and right ventricular hypertrophy. The leads considered are five in number and range from the superior vena cava to the inferior vena cava with leads from the intervening right atrium. These five points can be assumed to lie practically in a frontal plane of the body which passes through the center of the heart. That in turn permits us to work out the derived electrocardiograms from the frontal vectorcardiogram made according to the method used for the spatial vectorcardiogram.

The respective orientation of the unipolar axes was established by orthodiagraphy which was done at the time of the venous catheterization.

The results of the comparisons are very satisfactory, as shown by the tracings in figure 8. It

may be said, therefore, that the hypothesis of an instantaneous resultant of successive vectors of QRS-T and of a point of origin common to all of them is upheld by this example. The fact that unipolar tracings are recorded from the proximity of the heart and even from the interior of the atrial cavity does not impair the validity of the chosen hypothesis.

Discussion

The majority of comparisons of real and derived electrocardiograms calculated from spatial vectorcardiograms show remarkable agreement in normal subjects as well as in patients with cardiac disease. Faced with these facts it is possible to accept in a general fashion the comparison which relates the successive electrical fields created by the heart to a series of electrical fields created by successive resultant dipoles placed in a homogeneous conducting medium. The fact that examples are shown in which the position of the dipole varies with the time does not weaken this last statement.

Thus, to a great extent, the hypothesis stated at the beginning of this paper is upheld. It has been shown that exploration close to the heart, on the precordium or inside the thorax most often does not contradict the same conception. The hypothesis maintains its validity in extreme circumstances which, a priori, seemed incompatible. These conclusions are obviously a matter of personal evaluation. Since the complete data are given for every example, our results can be readily re-examined by the reader and the adopted criteria submitted to discussion. The requirements adopted to define concordance are not limited just to analogies but rest upon strict analysis of the chronology and the values of the potentials at every point. In order to arrive at this result the greatest amount of attention has been paid to all the technical details, which are so important in this type of work.

It has been shown that the vectorcardiographic method of the trirectangular trihedron gives remarkably constant results. This method, amply expounded and discussed by us and others,[2, 6, 13] offers a certain number of real and theoretic advantages but presents at the same time certain difficulties in its application. For example, it is not always possible to guarantee that the four points are equidistant from the anatomic cardiac center. Certain subjects, because of their anatomic shape, make the measurements particularly difficult. Lastly, even admitting a correct geometric application, the inequalities of the body's conducting medium is a matter of fact and constitutes always an unpredictable factor of minor discrepancy.

Each method presents some errors and unknowns. Undoubtedly, vectorcardiographic processes, using one or several leads close to the heart, easily bring about distortions of the spatial vectorcardiogram for which several reasons are brought out clearly in the exposition of the data reported in this paper. The use of the limbs in vectorcardiographic leads, as in Wilson's tetrahedron[15] for example, necessitates again reservations in some respects: the inequality of the distance from the heart to the shoulders[16]; the lack of precision of the points of application occasioned by ill-defined points of junction of the limbs with the torso.

Having made these reservations, it is not possible for us to evaluate the relative merits of the different vectorcardiographic methods employed at the present time when used for comparative studies like the present one, since until now this has been done only on the basis of the trihedron. Recently, Milnor and coworkers[17] have stated that the differences are sometimes considerable.

Efforts should be made toward obtaining an "ideal" spatial vectorcardiogram; that is, toward the realization of a spatial curve which would approach as closely as possible one that could be made at a distance from the heart, beyond the limits imposed by the confines of the human body. This hope appears to be utopian for the moment, and one must be content with less satisfactory approximations which perhaps would not meet with the approval of the physicists. This goal is precisely the goal which has guided Burger[11, 12] in his research.

The second point of discussion concerns the discrepancies observed in the course of our comparisons. Example 4 (fig. 7) is a characteristic one. One may think that the irregularity of the conducting medium of the body and the nonspherical form of the trunk, when definite cardiac hypertrophy is present, are responsible

for such discrepancies. A careful study of the collected tracings shows that the objection is not a valid one. In fact, this example makes it appear that the hypothesis of a single instantaneous resultant vector is no longer applicable for a short period of time, that which corresponds to vectors QRS 3, 4, 5, and 6. For all the other vectors collected, the hypothesis of a single instantaneous cardiac vector can be admitted. One cannot attribute this discrepancy to the medium of the body since its form and its conductivity are the same in both circumstances.

This consideration leads us to resort to another explanation, since the hypothesis of a simple electrical field emanating from a single dipole is no longer admitted under certain conditions. It has to be replaced by the hypothesis of a complex electrical field emanating from several synchronous dipoles placed at different points. By putting this problem in a simplified theoretic form, allowing for two instantaneous component vectors, we have shown[18] that under particular conditions and for certain points which are more or less close to the heart, the hypothesis of a unique resultant cannot be upheld.

At the instants displaying discrepancies, it seems as if two or several distinct cardiac territories are promotors of vectors of rather equal value and oriented in such a manner that one of these territories with respect to the exploring electrode exerts a predominant influence which masks the effects arising in all or several of the other territories. In the example discussed, a dominating influence of this type can be seen to exert itself still on points relatively removed from the heart, as V_{6R} for instance.

This hypothesis, introduced to cover certain discrepancies, presents nothing unusual since it has been suggested, in fact admitted, in electrocardiography to give support to the view that precordial leads mainly record the potential variations arising in the portion of the heart near to the electrode. The example of right bundle branch block (fig. 5) clearly expresses the variable influence caused by the nearness or the distance of the various territories of the heart with respect to a given point of the body. However it is difficult to understand why this influence is not noted under all circumstances in the normal subject and also in the proved examples of cardiac hypertrophy not reported here. It is probable that the balance between opposite potentials in the heart itself, upon which Wilson[19] has so strongly insisted, very often annuls electrical effects simultaneously arising from two or more territories.

The vast chapter of myocardial infarction poses several distinct vectorcardiographic problems which are not illustrated in this paper. Referring to the comparisons already worked out in such cases, it appears that injury vectors deserve consideration according to their spatial direction and anatomic location. Unilocular, plurilocular or extensive areas of infarction may lead to different hypotheses with respect to their representative vectors, fixed, mobile, single or multiple.

Our actual knowledge of the constitution of an electrical field created by a single dipole and its precise evaluation brings hope for better accuracy in the matter of localization for infarctions as well as for other focal events. One of our examples is of interest in this connection. It concerns the normal case illustrated in figure 3 where a displacement of the electrical center in the course of QRS can be inferred. For example, it can be noted that at the beginning of the QRS loop, the positions of the centers *A* and *B* correspond approximately to the region of the interventricular septum.

In conclusion, the practical application of vectorcardiography is justified on condition that the principles and limits of the method are well established and its significance exactly defined. The physiopathologic clarifications that it has already contributed, when used under rigorously controlled conditions, assures it a better place than that of an empiric process.

Summary

1. The bases and conditions for the realization of a correct vectorcardiogram are put forth.

2. A method for recording the spatial vectorcardiogram is proposed; this method makes use of a trirectangular trihedron.

3. The hypothesis of a homogeneous conducting volume is accepted for the present research.

4. A method is proposed to compare the real electrocardiogram and the corresponding scalar electrocardiogram derived from a vectorcardiogram registered in accordance with a trihedron process. These comparisons are very satisfactory for a whole series of points on the surface and inside the trunk. The evaluation of the comparisons is based on the chronology and voltage of the tracings.

5. One hundred and two normal and pathologic cases have been used for these comparisons. Six representative cases serve as illustration for this paper: two normal subjects, one with right bundle branch block, one with mitral stenosis, one with posterior infarction and one with chronic pulmonary disease.

6. The comparisons are carried out by using the standard, unipolar limb, precordial, various thoracic, esophageal and intravascular (venae cavae and right atrium) leads.

7. According to the examples, several hypotheses are advanced and verified: (a) that of an instantaneous resultant vector with a fixed point of origin located within the heart during all of QRS-T; (b) that of an instantaneous resultant vector whose point of origin moves within the heart as a function of the time; (c) that of two or several synchronous instantaneous vectors which, under certain circumstances, exclude the idea of a single resultant.

8. Electrodes placed close to the heart furnish most often electrocardiograms which also are in agreement with the hypothesis of an instantaneous resultant, as is true for points more distant from the heart.

9. The heterogeneity of the body conducting medium plays a minor role in the observed discrepancies. The distance to the heart from every lead point determines the amplitudes of the potentials which generally agree with the physicomathematical predictions imposed by a regular electrical field.

10. The application of vectorcardiography can and must be founded upon exact physical bases, several of which are presented in this paper.

Acknowledgments

The expenses occasioned by this research have been borne by a gift from private donors. We extend to these persons our warmest thanks. We are greatly indebted to Mr. E. Gay for the excellent execution of the figures and designs which illustrate this paper. Mr. H. White helped us with the English version.

REFERENCES

[1] Sulzer, R., and Duchosal, P. W.: Principes de cardiovectographie II. La stéréographie. Cardiologia **9:** 106, 1945.

[2] Duchosal, P. W., and Sulzer, R.: La Vectocardiographie. Basel, Karger, 1949.

[3] Schellong, F., Heller, S., and Schwingel, G.: Das Vektordiagramm, eine Untersuchungsmethode des Herzens. Ztschr. f. Kreislaufforsch. **29:** 497, 596, 1937.

[4] Duchosal, P. W., Grosgurin, J. R., and Sulzer, R.: Etude des relations entre le vectocardiogramme et les dérivations standard, unipolaires des membres et précordiales. Acta Cardiol. **3:** 273, 1948.

[5] —, —, and —: Etude des relations entre le vectocardiogramme et les dérivations précordiales. Bull. acad. méd. Paris **132:** 523, 1948.

[6] —, —, and Grosgurin, L.: Prévision de l'électrocardiogramme unipolaire en un point intérieur du corps humain au moyen du vectocardiogramme spatial enregistré à la périphérie, à distance du coeur. Acta Cardiol. **4:** 425, 1949.

[7] Wilson, F. N.: The distribution of the potential differences produced by the heart beat within the body and at its surface. Am. Heart J. **5:** 598, 1929–30.

[8] —, Macleod, A. G., and Barker, P. S.: The distribution of the currents of action and of injury displayed by the heart muscle and other excitable tissues. Ann Arbor, University of Michigan Press, 1933.

[9] —, and Bayley, R. H.: The electric field of an eccentric dipole in a homogeneous spherical conducting medium. Circulation **1:** 84, 1950.

[10] —: Personal communication, 1949.

[11] Burger, H. C., and Van Milaan, J. B.: Heart vector and leads. Brit. Heart J. **8:** 157, 1946; **9:** 154, 1947; **10:** 229, 1948.

[12] Becking, A. G. Th., Burger, H. C., and Van Milaan, J. B.: A universal vectorcardiograph. Brit. Heart J. **12:** 339, 1950.

[13] Cabrera, E., and Sodi-Pallares, D.: Factores que intervenien en la amplificacion de las derivaciones bipolares y su aplicacion a la vecto-

cardiografia. Arch. Inst. cardiol. México **19:** 91, 1949.

[14] Grosgurin, J. R., and Duchosal, P. W.: Les déplacements du "centre de gravité" des charges électriques pendant le segment ST. First International Cardiological Congress, Paris, France, September 4, 1950. In extenso in Arch. Inst. cardiol. México **20:** 662, 1950.

[15] Wilson, F. N., Johnston, F. D., and Kossmann, C. E.: The substitution of a tetrahedron for the Einthoven triangle. Am. Heart J. **33:** 594, 1947.

[16] —, Bryant, J. M., and Johnston, F. D.: On the possibility of constructing an Einthoven triangle for a given subject. Am. Heart J. **37:** 493, 1949.

[17] Milnor, W. R., Genecin, A., Talbot, S. A., and Newman, E. V.: The spatial vectorcardiogram and its relation to the precordial ECG. First International Cardiological Congress, Paris, France, September 4, 1950.

[18] Grosgurin, J. R., and Duchosal, P. W.: La notion de résultante en vectocardiographie. Acta Med. Scand. to appear in Suppl. 1952.

[19] Wilson, F. N., Macleod, A. G., and Barker, P. S.: The form of the electrocardiograms III. Opposed potential differences. Proc. Soc. Exper. Biol. & Med. **27:** 589, 1929–30.

The Value of High Fidelity Electrocardiography Using the Cathode Ray Oscillograph and an Expanded Time Scale

By PAUL H. LANGNER, JR., M.D.

The cathode ray is practically free from inertia and therefore an ideal instrumentality for studying variations in electrical potential. A cathode ray oscilloscope with an amplifier system of high frequency response and an expanded time scale, 330 mm. per second, were employed to record electrocardiograms. Such tracings revealed considerable notching, slurring, and other peculiarities not seen in the conventional electrocardiographic records on the same individuals. An instrument should have a frequency response curve flat to well over 330 cycles per second to record faithfully the human electrocardiogram. This is much higher than the frequency response of instruments usually used for electrocardiography.

THE CATHODE ray oscillograph and the high speed camera are presented as a method for the more detailed study of electrocardiographic patterns. The cathode ray oscillograph has been used in electrocardiography chiefly to study the vectorcardiogram or QRS and T loops. Our study is concerned with the use of the cathode ray oscillograph together with a high speed camera to record the standard extremity and precordial leads. Records obtained with this method reveal a wealth of detail that remain obscured in the conventional electrocardiographic record. Whether this additional detail will prove to be of value in routine electrocardiography has not yet been determined and will require considerable study. However, it seemed worth while now to present a brief account of the results obtained with this method and to report upon the application of this method to a particular field of investigation for which it seems eminently suited. This field is the study of electrocardiographic patterns and their distribution throughout the body and on its surface.

In order to exploit the advantages of the cathode ray oscillograph, the time scale must be greatly expanded. This is done by increasing the speed with which the recording paper moves from the usual 25 mm. to 300 mm. per second or more. The vertical amplitude of the record is also increased proportionately by increasing the amplification so that 1 mv. can be made to give a deflection of 6 cm. instead of the conventional 1 cm. The apparatus used for this study consisted of Dumont Cathode Ray Oscilloscope, type 304H, using the D-C amplifier and a Sanborn preamplifier* built especially

From the Medical Department of the Provident Mutual Life Insurance Company, Philadelphia, Pa.

* The following description of the preamplifier was supplied by Dr. Arthur Miller:

The amplifier preceding the Dumont oscilloscope is a two stage battery-operated device whose first stage uses a conventional push-pull circuit in order to provide for a true differential input. The first stage is then direct coupled to the second stage, which is also arranged in a push-pull circuit. The output of one plate of this second stage tube is condenser-coupled to the oscilloscope input. The coupling network also includes a phase correction circuit so that the response to a suddenly applied constant voltage (the decay curve) will show an initial plateau lasting for about 0.5 second. This form of decay curve is entirely adequate to record even the slowest variations of the cardiac voltage without distortion. (Since the oscilloscope's own amplifier is direct coupled throughout, the low frequency behavior of the complete system is determined entirely by this coupling network between the preamplifier and the oscilloscope.)

As pointed out above, the oscilloscope is coupled to only one of the plates of the preamplifier output stage. The second plate is ignored because the commercial version of the 304 Oscilloscope has only a single ended input. Although this means that half of the preamplifier output is not used, the gain of this preamplifier is sufficient to provide an over-all sensitivity of at least two inches of oscilloscope deflection per millivolt input to the preamplifier. In addition, the in phase response of the preamplifier is so attenuated by its own pair of cascaded push-pull stages

for this oscilloscope. The oscilloscope trace was photographed by a Westinghouse Oscilloscope Camera, Model ph 33671–1, using Kodak Linagraph paper No. 697. This type of instrumentation is widely used by neurophysiologists for recording action potentials in nerves but it has received scant attention in the field of electrocardiography. The use of a considerably expanded time scale revealing increased detail has been reported previously by Groedel[1] and Reid and Caldwell.[2] Recently a cathode ray oscillograph made expressly for electrocardiography has become commercially available, but since it uses the conventional time scale and limited amplification it is not comparable to the instrument which is the subject of this report. Gilford[3] used the cathode ray oscillograph and a Fairchild camera for recording electrocardiograms. He observed increased detail in the tracings but concluded, after a limited study, that it did not contribute significantly to clinical interpretation. He also concluded that a frequency response flat to about 200 cycles would give faithful recording for most human electrocardiograms.

Material

Records were obtained from 36 apparently normal individuals without history, symptoms or signs of cardiovascular disease. Their ages ranged from 20 to 65 years. As a routine, leads I, II, III, aV_R, aV_L, aV_F, V_1, V_3 and V_5 were recorded. In some instances additional precordial leads V_2, V_4 and V_6 were also recorded. Tracings were made with the subject recumbent in an electrostatically shielded and grounded room. Ten thousand ohm resistors were used in taking the "unipolar" extremity leads and the precordial leads. The subject must be free from tremor and completely relaxed; otherwise, skeletal muscle potentials will grossly distort the record. The film speed was 330 mm. per second.

Analysis of Results

To illustrate the results obtained by this method, tracings are reproduced (figs. 1 to 5), and certain generalizations about the characteristics of the records are made.

The T waves were essentially similar to those in conventional records. There was no notching or other hidden detail. Therefore, we shall not discuss the T wave further, and to conserve space this wave will be omitted from the illustrations.

The P waves showed a greater degree of notching than that seen in the conventional tracings from the same individual. An evaluation of these findings will not be attempted now. However, it seems that this method may be a useful tool for the study of auricular excitation.

This paper will be devoted entirely to a study of the form of the QRS complexes. In this small series of 36 cases, results must be preliminary and conclusions tentative, but certain definite tendencies seem to be clear. In the conventional electrocardiogram it is customary to accept as normal notching or slurring in all leads of low amplitude and in leads of large amplitude when the notching or slurring is near the isoelectric line. Therefore, we decided to accept the same criteria for cathode ray oscillograph tracings and, in addition, to scrutinize with special care those areas where notching and slurring usually do not occur in conventional tracings, namely leads of large amplitude in the two-thirds of the complex farthest from the isoelectric line.

Extremity Leads

Six extremity leads were obtained from each subject (I, II, III, aV_R, aV_L, aV_F). First, the three largest leads from each individual, a total of 108 leads, were examined. None of these leads made with the conventional electrocar-

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that the interference-rejecting properties of the system are not seriously affected by the single ended, rather than push-pull, connection between the amplifier and oscilloscope.

The high frequency performance of the complete preamplifier oscilloscope system can be measured either in terms of the "deflection time" in response to a square wave, such as a standardization pulse, or in terms of the "frequency response curve." The former method is commonly employed in describing electrocardiographs, and deflection times of the order of 7 to 10 milliseconds are common. The corresponding frequency response curves show substantial loss of response by the time 100 cycles is reached in the conventional electrocardiograph.

In the case of the system described here the deflection time is so short that it can not be measured with the paper speed at 330 mm. per second. The frequency response curve is substantially flat to at least 1000 cycles, so that the deflection time is actually less than 0.5 millisecond.

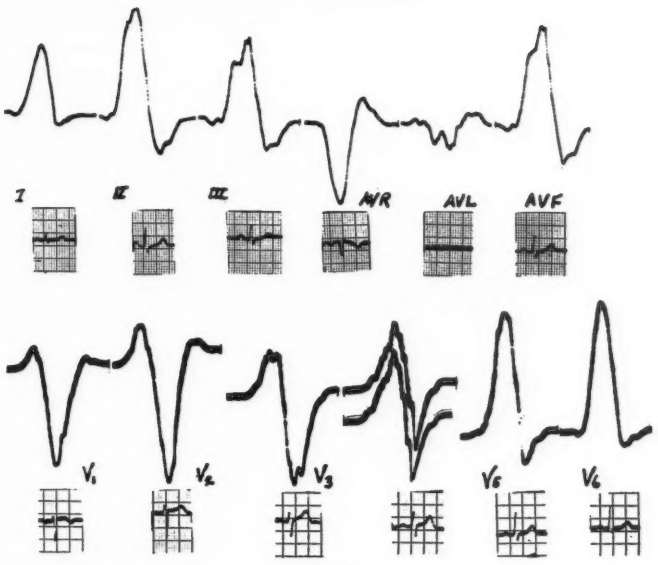

FIG. 1

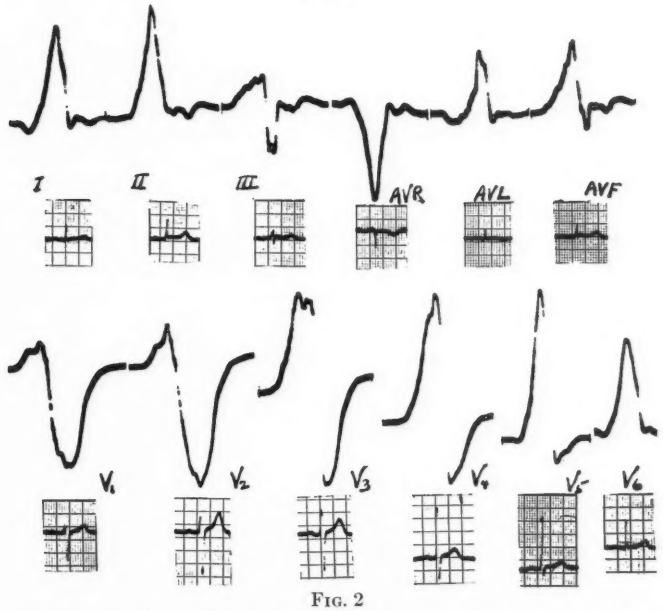

FIG. 2

FIGS. 1 and 2. Normal subjects. The leads are labeled. Only the QRS is shown in the cathode ray oscillograph record to conserve space. Immediately below each QRS is the P-QRS-T of the same lead made with the conventional electrocardiograph. In leads V_3 and V_4 of figure 2 the intrinsic-like deflection descends with such speed that it is not clearly registered in this photograph. All of the notching and slurring of these leads are true components of the deflections. None are artefacts or due to somatic muscle tremor. These distinctive notchings and slurrings of the leads were present to the same degree in all complexes of the lead and the base line was quite smooth in both these cases. Two successive oscilloscope tracings of V_4 in figure 1 are mounted to demonstrate that the notching and slurring are constant and not due to artefacts.

diograph showed notching or slurring. However, 46 of these same 108 leads made with the cathode ray oscillograph and expanded time scale showed definite notching or slurring. The major deflection of the QRS in the leads of greatest amplitude was entirely smooth in the cathode ray oscillographic records in 30 of the 36 individuals, but in the six other cases exhibited one notch or slur. Two of the six exceptions are shown in figure 3.

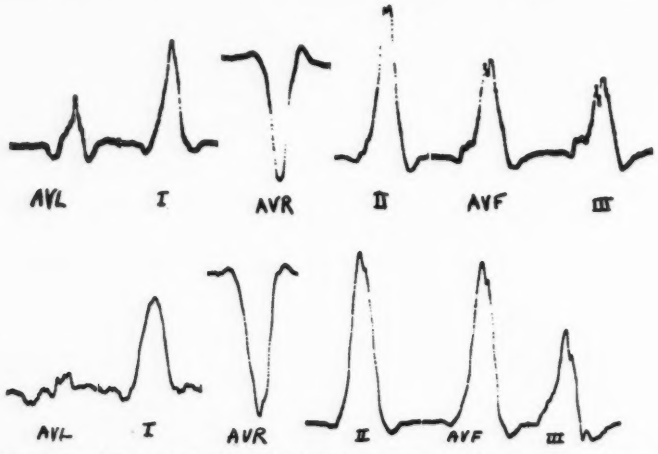

FIG. 3. This figure shows the six limb leads in two normal subjects where the major deflection of the QRS in the lead of greatest amplitude was notched. These leads are arranged in order from aV_L to III according to their position in the hexaxial reference system.

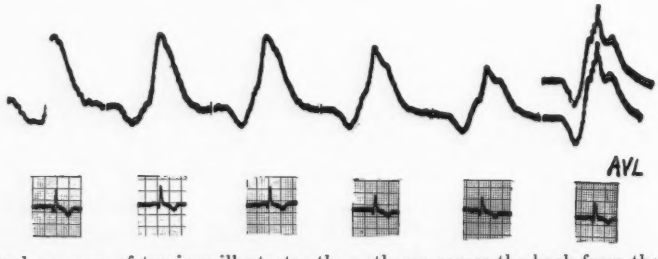

FIG. 4. The lower row of tracings illustrates the pathway across the back from the sixth dorsal spine to the left arm over which the contour of the pattern obtained with the conventional electrocardiograph remained constant. The upper row of tracings are the QRS complexes from cathode ray oscillograph records, each one taken from exactly the same electrode position as the tracing shown below. Careful inspection of the cathode ray oscillograph tracings will reveal that, while all of the tracings consist of qR deflections with a constant q/R ratio, each tracing is different from the others and aV_L differs most markedly from the others. Two successive oscilloscope tracings of aV_L are mounted to demonstrate that the peculiar wave form is constant and not due to artefacts.

A great majority of the tracings in this group had the largest limb lead deflections in leads II or aV_R which is equivalent to saying the mean electrical axis was most commonly between 60 and 30 degrees. (See table 1.) Since leads II and aV_R were frequently the largest deflections, this may account for the fact that they showed the greatest freedom from notching and slurring. However, as indicated in tables 1 and 2, although lead II was most frequently the largest deflection, lead aV_R was most frequently free from either notching or slurring. In five cases where the axis was +60 degrees, lead II showed notching or slurring whereas lead aV_R was free from these changes in the same individual. Another fact that is

brought out by tables 1 and 2 is that, while aV_F in this series is larger than lead I in a majority of cases, lead I shows much lower incidence of notching and slurring than aV_F. A

TABLE 1.—*Distribution of Mean Electrical Axis to Nearest 30° in 36 Normal Individuals*

Axis	Incidence
−30°	1
0°	2
+30°	10
+60°	19
+90°	4

TABLE 2.—*Notching and Slurring in the QRS Complex of the Six Extremity Leads recorded by the Cathode Ray Oscillograph in 36 Normal Individuals. Figures refer to the two-thirds of the largest deflection farthest from the isoelectric line in any given QRS*

Lead	Per Cent Having No Notch or Slur	Per Cent Having One Notch or Slur	Per Cent Having More Than One Notch or Slur
aV_L	3	14	83
I	61	17	22
aV_R	83	17	0
II	67	28	5
aV_F	22	22	56
III	6	11	83

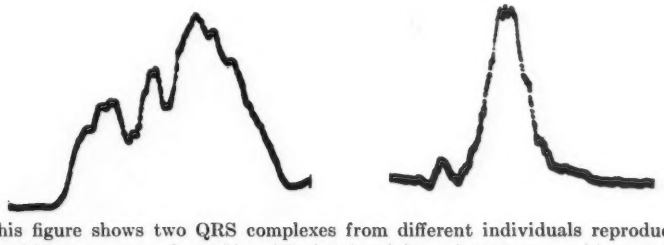

FIG. 5. This figure shows two QRS complexes from different individuals reproduced in their original size to illustrate unusual notching. The left hand figure is V_2 from a subject with right bundle branch block.

larger series of cases including a number of normal individuals with marked right or left axis deviation will be necessary to determine whether the direction of the mean electrical axis has a constant relation to the degree of notching or slurring encountered in the various limb leads. In this series lead aV_R showed the lowest incidence of notching or slurring, regardless of the direction of the mean electrical axis. A summary of the cathode ray oscillograph records showing no notch or slur or only one notch or slur in the QRS complex is given in table 2. These figures refer to the two-thirds of the major deflection of the QRS farthest from the isoelectric line. This criterion was used because notching and slurring are accepted as normal in the initial and terminal portions of the QRS in most instances, even in conventional records.

Precordial Leads

In 31 cases there was no close resemblance between any precordial lead and any one of the extremity leads. In five cases where close resemblance did occur it was in instances where both leads were free from notching, slurring, or any other characteristic detail.

Table 3 shows the characteristics of the precordial leads. It will be seen that notching and slurring were much more common in the precordial leads V_1 and the transitional zone complex than in the limb leads of large amplitude. However in V_5 and also in V_6 neither notching nor slurring occurred in any lead in the two-thirds of the complex farthest from the isoelectric line with two exceptions and in these the imperfections were minor.

TABLE 3.—*Characteristics of Precordial Leads in 36 Normal Individuals*

	V_1	Transitional Zone Complex	V_5
Notched	20	10	
Slurred	5	12	2
No notch or slur	11	15	34
Broad peak		2	
Broad nadir	12	5	

Electrocardiographic Pathways

One immediate field for investigation in which the expanded cathode ray oscillograph tracings should prove useful is in the relationship of the limb leads to the precordial and esophageal leads. Judging from records of standard precordial positions the various patterns are more different and distinctive than the conventional records. This will permit their identification as separate entities more accurately. Thus we can better determine the relationship of complexes written by different "views of the myocardium" and determine how these patterns contribute to the more remote body surface patterns, especially those of the extremity leads. In this way we can determine more precisely how the cardiac action currents are distributed in the body and on its surface. Wolferth, Livezey and Wood[4] have shown how patterns of potential variation are distributed on the body surface and have demonstrated pathways over which the contour of patterns is uniform and only decrement of the voltage occurs. These investigators used an electrode over the spine of the right scapula as their reference electrode. Myers and Klein,[5] using a central terminal as a reference electrode, concluded, "If a sufficient number of semidirect leads were taken, the counterpart of the QRS-T pattern of each of the unipolar limb leads could be demonstrated in a precordial or esophageal lead and a pathway along which the QRS-T complex maintained a fairly uniform configuration could be found bridging the gap between the extremity and the point on the thorax near the heart where the corresponding semidirect lead was obtained."

We studied the question of pathways as follows. Using the central terminal as a reference electrode, and a conventional direct-writing electrocardiograph, a pathway was located over which the contour of the patterns was uniform from a point on the thorax such as C_5 to an extremity. Sometimes these pathways occurred on the anterior body surface or axillary areas; sometimes it was necessary to explore the posterior surface of the body. In any case only one narrow pathway could be found over which all characteristics of the patterns of the QRS-T complexes except decrement remained uniform from a certain point on the thorax to the extremity. Great care must be taken that all leads for a given pathway be taken with the body in exactly the same position and in the same phase of respiration. Four individuals were selected in whom pathways over which the QRS-T pattern from points on the thorax to each extremity respectively remained uniform in contour as recorded by the conventional direct writer. We discovered that it was not possible to find such pathways in which the patterns were uniform in contour in all individuals. In each of these individuals, once such a given pathway was established, tracings were immediately made from exactly the same points, with the body in the same position and phase of respiration, using the cathode ray oscillograph and expanded time scale. This procedure was employed for pathways to each of the three extremities in four subjects, a total of 12 pathways. In all cases each pathway as recorded by the conventional direct writer showed patterns of uniform contour, varying only in voltage due to decrement. However, when the records of the cathode ray oscillograph were examined for a given pathway there was definite change from one complex to another due to notching, etc., or actual change in wave form. These changes were obscured in the conventional tracing. The result of an experiment is illustrated in figure 4.

Discussion

Of the extremity leads, I, aV_R, and II showed the least notching and slurring and of all the six leads aV_R was most commonly "smooth." One explanation of this finding in II and aV_R is that these were most commonly the largest deflections. But such an explanation would not also account for the frequent smoothness of I as compared with the usual notching in aV_F, since aV_F was on the average larger than I. The fact that the potential variations of the right arm contribute equally to leads I, aV_R and II may have some bearing on the problem. To elucidate this further would require study of more normal individuals with marked right and marked left axis deviation.

The precordial leads revealed wave forms, notching and slurring that were not apparent

in the conventional records. The clinical value of this wealth of detail remains to be established. One outstanding finding is the consistent lack of notching and slurring in V_5 and V_6, as contrasted to the other precordial leads. This may prove to be of diagnostic value in distinguishing normal from pathologic records.

In the lower row of tracings illustrated in figure 3 there is a notch near the peak in lead II. The width of this notch is less than 1 mm. at its base. Since the time scale is 330 mm. per second, the electrical phenomena causing this notch have a duration of less than 3 milliseconds. Therefore, an electrocardiograph should have a frequency response of well over 330 cycles per second to give a faithful recording of this type of deflection.

In the study of pathways over which the contour of a pattern remains constant we selected the central terminal as a reference electrode. Therefore, our results have no bearing upon the findings of Wolferth, Livesey and Wood.[4] When the central terminal is used the failure to demonstrate a pathway over which a given pattern remained constant from a point near the heart to an extremity is not surprising. Had the pattern remained constant in all its detail it would have been a coincidence because the body, though nonhomogeneous, is a volume conductor. Therefore, the potential variations of an extremity are the resultant summation of all the various patterns of potential variation which reach the extremity over the body surface and through the body tissues. Another possible explanation for the failure to obtain a pathway over which the pattern contour remained constant is that the central terminal may have deviated significantly from field zero potential.

This study was not an attempt to reach any conclusions about distribution of patterns but only to show the possibilities of the cathode ray oscillograph in this field. Patterns which look approximately the same in the conventional records may vary significantly in cathode ray oscillograph records because of characteristic detail such as notching, slurring, beading, speed of ascent or descent of the deflection, broad or flat peak or nadir, or contour not adequately described by any of these terms. It is not known what significance these differences between the conventional and expanded cathode ray oscillograph records may have in clinical diagnosis but it would seem that an electrocardiograph with higher fidelity and more expanded time scale than the instruments commonly used today would be desirable for fundamental investigative work.

Another field in which the expanded cathode ray oscillograph tracing should prove useful is the determination of whether all the significant details that can be obtained from records made from points close to the heart (such as V_2, V_3, and V_4 and esophageal leads) can be faithfully reconstructed from the spatial QRS loop. We believe this is an open question. For theoretic reasons which we have discussed elsewhere[6] it is possible that the QRS loop recorded from electrodes relatively distant from the heart may not reflect with precision all the details present in records made from electrodes close to the heart, especially when the expanded cathode ray oscillograph tracing is used as the criterion. If such discrepancies exist their significance should receive careful study.

Summary and Conclusions

1. Electrocardiograms made by the cathode ray oscillograph and expanded time scale reveal considerable detail such as notching, slurring beading, and unique contour that is obscured in the conventional electrocardiograph. The findings in 36 normal cases are presented.

2. The value of this increased detail in routine clinical electrocardiography has not been determined and deserves further study.

3. The application of this method to the study of the distribution of body surface patterns is illustrated.

4. On the basis of these 36 normal tracings it is believed that an electrocardiograph should have a frequency response curve relatively flat to over 330 cycles per second and probably much higher in order to record faithfully the human electrocardiogram.

REFERENCES

[1] Groedel, F. M.: Das Elektrokardiogramm. Theodore Steinkopff, Dresden und Leipzig, 1934.

[2] Reid, W. D., and Caldwell, S. H.: Research in electrocardiography. Ann. Int. Med. **7:** 369, 1933.

[3] GILFORD, S. R.: High fidelity electrocardiography. Proceedings of Second Joint AIEE-IRE Conference on Electronics in Nucleonics and Medicine, New York, N. Y., October 31, 1949.

[4a] WOLFERTH, C. C., LIVEZEY, M. M., AND WOOD, F. C.: Distribution of Patterns of Ventricular Potential Which Determine Forms and Significance of Electrocardiograms. Am. J. M. Sc. **205:** 469, 1943.

[b] —, —, AND —: Studies on distribution of potential concerned in formation of electrocardiograms. Am. J. M. Sc. **203:** 641, 1947.

[5] MYERS, G. B., AND KLEIN, H. A.: The relationship of unipolar limb leads to precordial and esophageal leads. Am. Heart J. **35:** 727, 1948.

[6] LANGNER, P. H., JR.: The theory and practice of vector analysis in electrocardiography. Proceedings of the 38th Annual Meeting of the Medical Section of the American Life Convention, June 15, 1950.

A Technic of Vascular Catheterization with Small Plastic Catheters

Its Utilization to Measure the Arterial Pulse Wave Velocity in Man

By Truman G. Schnabel, Jr., M.D., Hugh F. Fitzpatrick, M.D., Lysle H. Peterson, M.D., William J. Rashkind, M.D., Daniel Talley, III, M.D., and Robert L. Raphael, M.D.

A method of vascular catheterization is presented in which small polyvinyl catheters are introduced into peripheral vessels through 18 to 21 gage needles and then advanced into the central vascular bed. This technic has been utilized in the study of hemodynamic events occurring in the central arterial vessels in man. The results obtained from 31 arterial catheterizations done in 21 subjects are reported. Utilizing this technic, it has been impossible to catheterize the pulmonary artery in man. However, the method has proved useful in the study of right atrial and central venous pressure changes.

CATHETERIZATION procedures used to study the vascular dynamics in man necessitate exposure of a vessel to permit introduction of the large caliber catheters currently in use. The development of the Lilly capacitance manometer has made possible the recording of peripheral intra-arterial pressures with small plastic catheters.[1] Central vascular pressures can be recorded through similar catheters which are longer but of sufficiently small caliber that they may be inserted into the vascular system through an 18 to 20 gage needle.[2, 3] This paper reports the use of this technic for venous and arterial catheterization and the results obtained during catheterization of the central and peripheral arteries in man.

Materials and Methods

Polyvinyl tubing, plain or impregnated with barium sulfate for radiopacity, is treated with ether or heat to make catheters with properties suitable for manipulation and for recording pressures. The manometric system used is identical with that described previously.[1] Blood samples can be drawn at rates up to 4 cc. per minute and have been analyzed by a micromethod described by Deering.[4] Catheters are inserted through needles of 18 to 21 gage with walls thinner than those of standard gage needles. For catheterization of the aorta, the brachial or femoral artery is punctured with a 19 gage needle and the catheter passed under fluoroscopic guidance to the desired site. For venous catheterization the same procedure is followed, using the external jugular, internal jugular,[5] basilic, or femoral veins as the entrance site for the catheter. Arterial and venous pressure curves are recorded simultaneously with lead II of the electrocardiogram. To calculate pulse wave velocity the catheter is moved through a measured distance in the vessel and this distance is divided by the difference in time of onset of the pulse at the two sites in relation to the Q wave of the electrocardiogram. The start of the arterial pulse is taken as that point at which the first detectable rise in pressure is noted. Recording paper speed was 125 mm. per second, allowing measurements to be made accurately to ±0.001 second. Subjects were fasting six hours and supine. Figure 1 is an example of the central aortic pulse contour recorded just distal to the aortic valve in a normal subject.

Results

Forty-one aortic catheterizations have been performed in 25 subjects. The results reported here cover 31 studies in 21 individuals. Subjects have ranged in age from a 5 week old infant to a 60 year old man, and may be

From the Department of Physiology, University of Pennsylvania, School of Medicine; and from the Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

This work was supported by a grant from the U. S. Public Health Service and by a contract between the Office of Naval Research of the Navy and the University of Pennsylvania (NR 160-058).

This work was done during the tenure of Research Fellowships of the American Heart Association held by T. G. S. Jr. and L. H. P. During the study, W. J. R. was a Post-Doctorate Fellow of the National Heart Institute, and D. T. III was a Fellow of the American Cancer Society.

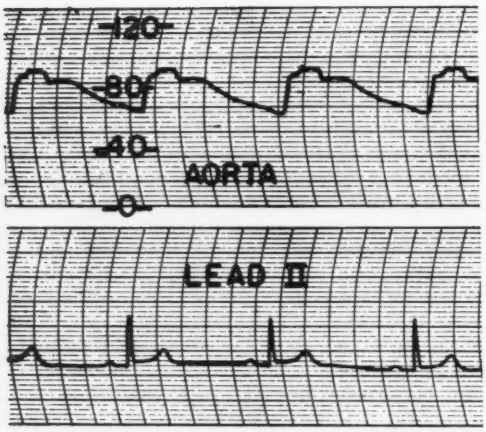

FIG. 1. A central aortic pulse recorded just distal to the aortic valve and a simultaneous electrocardiogram (lead II). Vertical time lines = 0.2 second.

grouped as follows: group I, 10 healthy men, 20 to 24 years old; group II, four healthy men, 25 to 34 years old; group III, two healthy men, 35 and 44 years old; and group IV, a heterogenous group, including two males with thrombosis of the lower segment of the abdominal aorta, an infant and an adult female with aortic stenosis, and a male with an anomalous right subclavian artery.

Table 1 shows the average pulse wave velocities and their ranges in the various arterial segments. The over-all averages of 16 normal subjects between 20 and 40 years of age show that the pulse wave velocity in the ascending and descending aorta is approximately 5 meters per second. The pulse wave velocities in the subclavian and axillary arteries as well as in the abdominal aorta are somewhat slower, being

TABLE 1.—*Average Pulse Wave Velocities (Meters per Second) and Their Ranges Obtained in Central and Peripheral Vessels*

	Ascending Aorta	Arch	Descending Aorta	Abdominal Aorta	Iliac	Subclavian	Axillary	Brachial	Valves to Femoral	Descending Aorta to Femoral	Subclavian to Brachial
Group I, 20–24 years, 10 individuals											
No. Deter.	1	1	16	10	10	8	8	8	1	10	8
Average PWV	4.2	3.1	5	4.3	7.7	4.1	4.0	8.6	4.2	5.4	5.5
Range PWV	—	—	3.8–6.3	2.9–5.4	5–10	3.2–5	3.6–4.5	7.1–11.1	—	4.7–6	5.2–6.7
Group II, 25–34 years, 4 individuals											
No. Deter.	2	1	4	4	4	1	2	2	1	4	2
Average PWV	5.6	4.7	5.0	4.6	8.8	4.5	4.9	6.5	5.3	5.7	5.6
Range PWV	4.5–6.7	—	4.7–5.9	3.6–5	7.1–10	—	4.5–5.5	6.3–6.7*	—	5.3–6	4.8–6.3
Group III, 35–44 years, 2 individuals											
No. Deter.	1	1	1	2	2	—	—	—	1	2	—
Average PWV	5.0	4.2	5.4	6.2	10.6	—	—	—	6.3	7	—
Range PWV	—	—	—	5.9–6.2	10–11.1	—	—	—	—	6.9–7.1	—
Group I, II, III, 16 individuals											
No. Deter.	4	3	21	16	16	9	10	10	3	16	10
Average PWV	5.0	4.0	5.1	4.6	8.4	4.2	4.2	8.2	5.3	5.7	5.5
Range PWV	4.5–5.6	3.1–4.7	3.8–6.3	2.9–6.2	5–11.1	3.2–5	3.6–5.5	6.3–11.1	4.2–6.3	4.7–7.1	4.8–6.7
AH, 43 yrs. old			4.5			4.0	10				6.2
SB, 69 yrs. old. Hypertension						5	4.5	12.1			7.6
AG, 34 yrs. old. Aortic Stenosis	4.8	3.8	3.6	4.9	7.25				4.8	5.1	
Baby S, 5 weeks. Aortic Stenosis			3.2	4							
AR, Aberrant Rt. Subclavian Artery						4.7	4.7	10			

* Recorded in proximal end of brachial artery only.

4.2 meters per second and 4.6 meters per second, respectively. There is a marked increase in the velocity of the pulse wave in the brachial and iliac arteries where it averages 8.2 meters per second, and 8.4 meters per second. The over-all pulse wave velocity from the aortic valve to the femoral artery is 5.3 meters per second, and from the subclavian to brachial artery 5.5 meters per second. In group IV the infant's pulse wave velocity is somewhat slower, whereas the 69 year old patient with arteriosclerosis has the fastest pulse wave velocity found in the brachial artery. The findings in the adult female with aortic stenosis are within the normal range. Average figures for each group show a gradual rise in the pulse wave velocity with increasing age.

Figure 2 is a plot of the velocities of consecutive 10 cm. aortic segments in 13 of the 16 normal individuals. Three cases are not included because of incomplete data. All 13 individuals show a minimum pulse wave velocity in the region of the diaphragm, in 11 instances within 5 cm. of the diaphragm, and in two cases 12 cm. below the diaphragm. Nine of 11 cases show a decrease in the pulse wave velocity in the axillary or subclavian arteries when compared with its speed in the descending aorta.

Table 2 shows the time difference between the Q wave of lead II of the electrocardiogram and the onset of the pulse in various parts of the arterial system. The first detectable rise in pressure at the aortic valves occurs on the average .085 second after the Q wave. The Q to brachial time averages .167 second and the Q to femoral time averages .205 second. Both show an inverse relation to age.

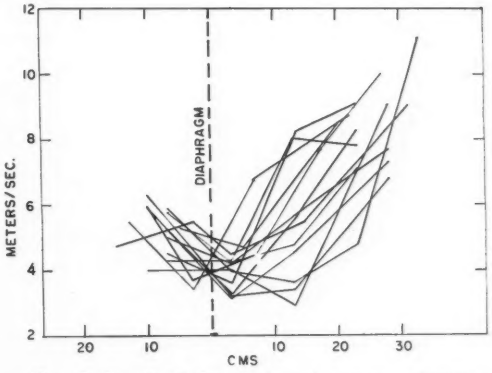

FIG. 2. Graph of the aortic pulse wave velocities in consecutive 10 cm. segments for 13 of the 16 normal individuals.

In most cases the sensitivity of the manometer was increased to permit magnification of the pulse contours, thus preventing measurement of diastolic pressures. In three individuals the systolic, diastolic, and mean pressures were recorded accurately (table 3). There is a general increase in the pulse pressure as the catheter

TABLE 2.—*Time Relations in Seconds between the Q Wave of Lead II of the Electrocardiogram and the Onset of the Pulse at Different Sites in the Arterial Tree*

	Q-Brachial	Q-Femoral	Q-Subclavian	Q-Carotid	Q-Aortic Valve
Group I					
No. Determinations	8	9	6	6	1
Average	.173	.211	.119	.112	.071
Range	.148–.192	.190–.237	.102–.141	.089–.130	
Group II					
No. Determinations	2	4	2		2
Average	.156	.201	.116		.089
Range	.141–.170	.183–.223	.101–.132		.077–.100
Group III					
No. Determinations	1	2	1		1
Average	.146	.189	.109		.092
Range		.183–.195			
Totals of Above 3 Groups					
No. Determinations	11	15	9	6	4
Average	.167	.205	.117	.112	.085
Range	.141–.192	.183–.237	.102–.141	.089–.130	.071–.100

progresses toward the periphery with no significant change in the mean pressure. In two instances the increased pulse pressure was primarily due to a rise in systolic pressure. In one instance the fall in diastolic pressure was equal to the rise in systolic pressure.

venous pressure curves in man. The simplicity of the procedure as well as the lack of trauma to the patient has permitted the repeated performance of right auricular catheterization in the same individual, utilizing one vein as the entrance site of the catheter.

TABLE 3.—*Systolic (S), Diastolic (D), Mean (M) and Pulse (P) Pressures Obtained in the Aortic and Iliac Arteries of Three Normal Individuals*

	I				II				III			
	M	S	D	PP	M	S	D	PP	M	S	D	PP
Ascending....	77	84	68	16	75	93	62	31	87	109	77	32
Descending...	75	84	63	21	77	96	62	34	82	107	72	35
Abdominal...	76	99	64	35	72	96	64	32	83	109	67	42
Femoral.....	76	103	62	41	76	113	59	54	87	118	70	48
Over-all.....	−1	+19	−6	+25	+1	+20	−3	+23	0	+9	−7	+16

DISCUSSION

The use of catheters with small diameters which may be inserted into an artery or vein through a needle eliminates exposure of the vessel and minimizes trauma to the vessel and subject. In addition the small space occupied by the catheter within the lumen of the vein or artery results in less interference with the dynamics of flow in the vessel. Valves, irregular cardiac chambers, and the acute angulation required for the catheter to enter the pulmonary artery are inherent sources of risk in this as in any cardiac catheterization. In a series of 40 dogs in whom right heart catheterization was done, 25 per cent showed small subendothelial hemorrhages in the right auricle or right ventricle. In one instance a mural thrombus was present in the right auricle, and on one occasion the catheter looped itself around a papillary muscle with its tip impinged under a leaflet of the tricuspid valve, making removal impossible. Fifty per cent of the dogs in whom the left ventricle was catheterized showed small ecchymotic areas on the leaflets of the aortic valves.

It had been hoped that this technic might be utilized to catheterize the pulmonary artery in man. Experienced gained during 20 venous catheterizations has shown that this is not feasible due to the difficulty encountered in manipulating a small catheter within the right heart. The technic has proved ideal, however, for the study of right auricular and central

The first three human subjects for aortic catheterization developed pain in the distal phalanges of the catheterized arm. Pain occurred three to four hours after completion of the procedure, reaching maximum intensity in eight hours and gradually disappearing over a two week period. Limiting the procedure to one hour and modifying the catheter production technic has lessened the frequency and severity of the symptoms. Except for occasional small hematomas, the only other complication noted was in the 69 year old man with arteriosclerosis and thrombosis of the terminal aorta. Five minutes following removal of the brachial catheter the brachial and radial pulsations were not present, the hand blanched, and the subject complained of pain and tingling in his hand. The pulsations returned to normal one hour later without treatment and no subsequent symptoms were noted.

Methods of determining pulse wave velocity used by Bazett,[6] Sands,[7] Hallock[8] and Haynes[9] necessitated the estimation of the length of the arterial segment. It was impossible with their technics to measure the velocity of the pulse in localized segments of the aorta or other central vessels. The method utilized in this paper permits the measurement of pulse wave velocities over small segments of the aorta, for the arterial segment is measured by the distance the catheter is withdrawn. This relation holds except for the arch of the aorta

where it has been assumed that the catheter follows the mean curvature.

The errors inherent in the method lie in the degree of accuracy with which the point of onset of the pulse curve can be estimated. With high paper speed, permitting the measurement of small time intervals, the onset of arterial systole is gradual. To minimize this source of error the time delay between the Q wave and the onset of the arterial pulse was averaged for five consecutive beats at each resting site of the catheter. In addition, mensurations in each case were made solely by one of the authors. Although the velocity of the pulse wave may be measured in a small segment of an artery, the possible error in the final determination increases markedly the shorter the segment and the faster the transmission time. Errors in measurements of the pulse curves of plus or minus .001 second allow an error of plus or minus 20 per cent in the final calculated pulse wave velocity in an iliac segment 10 cm. long. In central vessels, where the pulse wave velocity is slower, errors in measurements of the pulse curves may account for an error of plus or minus 10 per cent in the final calculated pulse wave velocity. In an effort to decrease the significance of these sources of errors, mean values for pulse wave velocities over the longest possible segments are reported in this paper.

The differences between the mean pulse wave velocity in the aorta and the mean velocities of the pulse in the brachial and iliac arteries are greater than 3 standard errors of the difference of the means and therefore highly significant. Pulse wave velocities of 8.2 meters per second and 8.4 meters per second in the brachial and iliac arteries, respectively, are slightly lower than figures reported by others of the pulse wave velocity from the femoral to the dorsalis pedis arteries and from the brachial to the radial arteries. The constant deceleration of the pulse wave velocity in the region of the diaphragm results in slightly lower mean values for the pulse wave velocity of the abdominal aorta as compared with that of the thoracic aorta. The difference between the means of the velocities of the pulse in these two areas is not significantly different but might become so were the series of cases larger.

These results indicate that a marked increase in the pulse wave velocity does not occur until the pulse reaches the brachial or iliac vessels and that the pulse wave velocity increases only slightly from the brachial and iliac vessels to the radial and dorsalis pedis arteries respectively. At the level of the diaphragm and in the subclavian artery there is a deceleration of the pulse wave velocity. This deceleration can be explained on the basis of (1) changes in regional distensibility of the vessels due to (a) intrinsic regional structural variations in the vessels, (b) difference in the extrinsic pressure exerted by surrounding tissues or organs, (c) changes from subatmospheric to atmospheric pressure; or, (2) changes near the ostia of large vessels such as the celiac and renal arteries.

In five instances the catheter was passed directly to the aortic valve permitting calculation of the pulse wave velocity over the entire aorta. The Q to aortic time averaged .085 second which is similar to the Q to pulmonary artery time reported by Coblentz.[10]

Conclusions

1. The use of small caliber catheters inserted through 18 to 21 gage needles for aortic and right heart catheterizations in man is reported. It has been impossible to catheterize the pulmonary artery in man by this method. However, the technic has proved useful in the study of right auricular and central venous pressure variations.

2. The pulse wave velocity is approximately 5 meters per second in the human aorta and 8 meters per second in the brachial and iliac arteries.

3. There is a deceleration of the pulse wave in the vicinity of the diaphragm and the subclavian artery.

4. The onset of left ventricular ejection follows the Q wave of lead II of the electrocardiogram by an average of .085 second.

5. The time from Q to brachial pulse averages .167 second; from Q to femoral pulse averages .211 second.

6. There is an increase in the pulse pressure from the aortic valve to the femoral artery.

The mean pressures over this segment shows no significant change.

Acknowledgments

The authors wish to express their gratitude to the late Dr. H. C. Bazett for his invaluable aid and assistance in this work. In addition we wish to thank Albert E. Afford and Henry C. Mellette for technical assistance in the development of a satisfactory way of making the catheters.

REFERENCES

[1] Peterson, L. H., Dripps, R. D., and Risman, C. G.: A method for recording the arterial pressure pulse and blood pressure in man. Am. Heart J. **37:** 771, 1949.

[2] —, Schnabel, T. G., Jr., Fitzpatrick, H. F., and Bazett, H. C.: Pressure pulses and pulse wave velocities in the aorta and large vessels of man as determined by direct methods. Am. J. Physiol. **159:** 585, 1949.

[3] Fitzpatrick, H. F., Schnabel, T. G., Jr., and Peterson, L. H.: A small plastic tubing technique for right and left heart catheterization Federation Proc. **8:** 46, 1949.

[4] Deering, R. C.: A constant delivery pipette particularly designed for analyses of small volumes. Federation Proc. **8:** 33, 1949.

[5] Hoover, W. B., and Lundy, J. S.: A technique for phlebotomy of the internal jugular vein. Proc. Staff Meet., Mayo Clin. **18:** 161, 1943.

[6] Bazett, H. C., and Dreyer, N. B.: Measurements of pulse wave velocity. Am. J. Physiol. **63:** 91, 1922.

[7] Sands, J.: Simultaneous cardiographic and electrocardiographic records in man. Am. J. Physiol. **67:** 203, 1923.

[8] Hallock, P.: Arterial elasticity in man in relation to age as evaluated by the pulse wave velocity method. Arch. Int. Med. **54:** 770, 1934.

[9] Haynes, F. W., Ellis, L. E., and Weiss, S.: Pulse wave velocity and arterial elasticity in arterial hypertension, arteriosclerosis, and related conditions. Am. Heart J. **11:** 385, 1936.

[10] Coblentz, B., Harvey, R. M., Ferrer, M. I., Cournand, A., and Richards, D. W. Jr.: The relationship between electrical and mechanical events in the cardiac cycle of man. Brit. Heart J. **11:** 1, 1949.

The Pulmonary Vascular Responses to Short-Term Hypoxia in Human Subjects

By JOSEPH T. DOYLE, M.D., JOSEPH S. WILSON, M.D., AND JAMES V. WARREN, M.D.

Using the catheter technic, the acute circulatory reactions to a brief period of hypoxia have been studied. It was found that when a normal person breathed a gas mixture containing only 10 per cent oxygen, the pulmonary arterial pressure rose but the pulmonary capillary pressure remained unchanged. This indicated pulmonary vasoconstriction, thought to be due to a direct effect on the pulmonary vascular tree. No demonstrable change in so-called pulmonary blood volume could be detected. In an additional group of patients with cardiopulmonary disease the reactions were more erratic but not significantly different in type.

IN CERTAIN patients with heart disease pulmonary hypertension occurs in association with a remarkably steep pulmonary arteriocapillary pressure gradient suggestive of a vasoconstrictive mechanism. It has been demonstrated in normal human subjects that acute hypoxia induces a considerable pulmonary hypertension,[1] but the mechanism of this has not been elucidated. It was thought desirable to make further observations on the mechanism of hypoxic pulmonary hypertension in normal subjects and in patients with cardiopulmonary disease with particular reference to the pressure gradient between the pulmonary artery and the pulmonary capillary bed and to possible changes in the pulmonary blood volume.

METHODS

Eight normal adults ranging in age from 27 to 45 years, and 12 individuals with sundry cardiopulmonary abnormalities have been studied. The subjects were either fasting or had had a light breakfast. Mild barbiturate sedation was occasionally employed to allay anxiety or to relieve respiratory distress. The recumbent position was used unless orthopnea required elevation of the shoulders.

A double lumen catheter was passed into the pulmonary artery by the usual technic.[2] The tip was wedged in an end vessel so that the pulmonary capillary pressure[3] was measured, while the proximal lumen opened into the main pulmonary artery. Simultaneous pressure measurements were made on Sanborn electromanometers and, together with an electrocardiogram and a pneumogram, were inscribed on a Sanborn Poly-viso recorder. A zero point 5 cm. below the sternal angle was arbitrarily selected for pressure measurement. A Cournand needle was inserted into a brachial artery. Blood gas analyses were done by the method of Van Slyke and Neill.[4] The oxygen consumption was determined by the open circuit method of Haldane.[5] The cardiac output was calculated by the Fick principle and also by the dye dilution method of Stewart[6] and Hamilton[7] as modified by Ebert.[8] A carefully measured amount of T-1824 dye was rapidly injected into the proximal lumen of the cardiac catheter and arterial blood was collected for two second periods during the primary circulation. In subjects with a prolonged circulation time the collecting period was suitably lengthened. The optical density of the dyed blood samples was read on a Beckman spectrophotometer. A time-concentration curve was then constructed from which were derived the mean circulation time of the dye, the cardiac output and the so-called pulmonary blood volume. A satisfactory correlation between the results of the direct Fick and of the dye dilution methods has been shown in this and other laboratories. We feel that the dye method is particularly useful and reliable in demonstrating directional changes in cardiac output. The general blood volume was estimated from a 10 minute dye sample, or in the case of subjects with a delayed mixing time, from multiple dye samples.

A BLB* oronasal mask was then applied to the face and 10 per cent oxygen in nitrogen was administered. Continuous or semicontinuous records

From the Departments of Medicine and Physiology, Emory University School of Medicine, and the Medical Service, Grady Memorial Hospital, Atlanta, Ga. J. S. W. is a Whitehead Foundation Research Fellow.

Presented in part at a meeting of the American Physiological Society, May 2, 1951, in Cleveland, Ohio.

This study was supported in part by a grant from the American Heart Association and by the U. S. Department of the Navy.

* Boothby-Lovelace-Bulbulian.

TABLE 1.—*Circulatory Responses to Hypoxia of Eight Normal Individuals*

Patient	Age	Surface Area	Remarks	Hematocrit Reading	Pulse Rate	Pulmonary Arterial Pressure			Pulmonary Capillary Pressure	Pulmonary Pressure Gradient	Systemic Blood Pressure			Arterial Oxygen Saturation	Mean Circulation Time	Oxygen Consumption	Arteriovenous Oxygen Difference	Cardiac Index		Stroke Volume	General Blood Volume	Pulmonary Blood Volume	PBV/GBV	Pulmonary Resistance	Right Ventricular Work	Total Peripheral Resistance	Left Ventricular Work
						Systolic	Diastolic	Mean			Systolic	Diastolic	Mean					Fick	Dye								
	(years)	(sq.M.)			(beats/min.)	(mm.Hg)			(mm. Hg)	(mm. Hg)	(mm.Hg)			(%)	(sec.)	(cc./min./sq.M.)	(cc./100 cc.)	(L./min./sq.M.)		(cc.)	(cc./sq.M.)	(cc./sq.M.)	(%)	(dynes sec./cm.^{5})	(Kg.M./min./sq.M.)	(dynes sec./cm.^{5})	(Kg.M./min./sq.M.)
1	45	1.63	Control	38.3	85	20	4	10.0	2.5	7.5	—	—	—	99	15.8	132	3.9	3.4	2.8	53	2780	730	26	133	0.40	—	—
			Hypoxia 14 min.	38.9	90	27	10	17.5	2.0	15.5	—	—	—	87	13.6	—	—	—	3.3	60	2830	750	27	226	0.83	—	—
2	36	1.76	Control	41.0	75	18	7	12.0	8.5	3.5	—	—	—	95	14.3	180	4.4	4.0	3.1	72	3370	730	22	53	0.53	—	—
			Hypoxia 12 min.	40.4	75	22	10	16.5	8.5	8.0	—	—	—	75	10.3	—	—	—	4.6	108	3480	790	23	80	1.09	—	—
3	28	1.73	Control	41.2	90	15	4	9.5	4.0	5.5	120	72	88	96	12.3	176	4.5	3.9	2.8	54	—	580	19	107	0.38	1425	3.6
			Hypoxia 13 min.	42.2	90	21	8	15.0	5.0	10.0	120	70	87	76	10.1	—	—	—	3.4	66	3030	570	19	133	0.73	1185	4.3
4	32	1.98	Control	45.5	75	14	6	10.0	5.0	5.0	122	73	92	96	9.7	164	4.2	3.9	3.5	93	2870	570	20	45	0.48	1052	4.4
			Hypoxia 11 min.	44.4	75	26	10	16.0	4.0	12.0	110	63	83	81	9.6	—	—	—	3.6	96	2830	580	20	133	0.79	919	4.1
5	41	1.67	Control	39.8	70	14	4	9.0	5.5	3.5	108	65	88	95	9.8	97	3.1	3.2	3.0	71	2380	490	21	53	0.38	1412	3.8
			Hypoxia 14 min.	39.6	80	21	8	13.5	3.5	10.0	110	68	90	76	9.5	—	—	—	3.5	73	2290	550	24	133	0.68	1239	4.5
6	27	1.86	Control	45.9	100	14	6	9.0	4.0	5.0	125	83	98	95	10.8	106	3.2	3.3	4.7	87	3040	840	28	45	0.61	906	6.6
			Hypoxia 15 min.	46.4	120	25	9	17.0	6.5	10.5	118	72	90	64	6.4	—	3.4	—	7.5	117	2980	800	27	60	1.83	519	9.7
7	41	1.94	Control	41.4	80	14	6	7.0	4.0	3.0	160	95	115	94	9.1	164	4.5	3.6	3.8	92	2810	580	21	32	0.38	1199	6.3
			Hypoxia 14 min.	42.3	100	18	7	12.0	5.5	6.5	150	75	105	66	6.8	—	2.8	—	5.2	101	2760	590	21	52	0.90	826	7.8
8	39	1.96	Control	38.8	70	17	7	11.0	6.0	5.0	130	85	108	93	13.0	102	4.1	2.4	3.3	96	2300	720	31	60	0.52	1288	5.1
			Hypoxia 14 min.	39.2	70	24	9	16.0	3.0	13.0	135	85	103	68	11.0	—	3.1	—	3.9	109	2350	710	30	137	0.73	1083	5.8
Avg.	36	1.82	Control	41.6	81	16	6	10.0	5.0	5.0	128	79	98	95	11.9	140	4.0	3.5	3.4	77	2810	660	24	66	0.46	1214	5.0
			Hypoxia		88	23	9	15.0	5.0	10.0	124	72	93	74	9.7	—	—	—	4.4	91	2810	670	24	119	0.95	962	6.0
Per cent change					+8%	+44%	+50%	+50%	±0%	+100%			−5%	−22%	−18%				+29%	+18%		+2%		+80%	+107%	−21%	+20%
p value					$.2 < p < .3$			$p < .001$		$p < .001$			$.3 < p < .4$	$p < .001$	$.05 < p < .1$				$.05 < p < .1$	$.1 < p < .2$				$p < .001$	$.6 < p < .8$	$.05 < p < .1$	$.3 < p < .4$

were kept of the respiration, heart rate, pulmonary arterial and pulmonary capillary pressures. At about 10 minutes the systemic blood pressure was measured and arterial blood was obtained for determination of oxygen saturation. The cardiac output and the pulmonary blood volume were then remeasured by the dye dilution technic.

Circulatory effects due to the mask itself or to a significant accumulation of carbon dioxide in the dead space were excluded by appropriate procedures.

The vascular resistance of the pulmonary and of the systemic circuits and the work of the ventricles were calculated by the formulas suggested by Dexter.[9]

Results

In the normal group (table 1) the inhalation of the low oxygen mixture was followed by a deepening of respiration without much increase in rate, a response characteristic of hypocapnic anoxia. No subject became significantly dyspneic. Cyanosis was only minimal. Wide respiratory variations were imposed on the pressure contours. Within a minute or so there was a rise in the pulmonary arterial mean pressure in which both the systolic and the diastolic pressures participated (fig. 1). On the other hand, the pulmonary capillary pressure was unchanged or fell slightly during the hypoxic period. The gradient of pressure between the pulmonary artery and the pulmonary capillary bed widened slowly and steadily during hypoxia (fig. 1). The systemic arterial pressure was unchanged or fell slightly. The average heart rate rose, although in several individuals there was no change. The circulatory velocity from pulmonary to peripheral artery increased. The cardiac output tended to increase, roughly in proportion to the degree of arterial oxygen unsaturation. The pulmonary blood volume, that is the volume of blood between the main pulmonary artery and all peripheral points temporally equidistant from the point of arterial sampling, was not significantly altered. There was a highly significant increase in the pulmonary vascular resistance, a less significant fall in the systemic vascular resistance, and some increase in the work of the heart.

In the abnormal group (table 2), the circulatory responses to hypoxia were so variable as to render a statistical comparison with the normal group of little value. Almost all of these individuals developed considerable air hunger and several became strikingly cyanotic. Those subjects (cases 1, 3, 8, 9) with an already elevated pulmonary arterial pressure and a correspondingly high pulmonary vascular resistance all showed a further increase in the pulmonary arterial pressure during hypoxia, while the pulmonary capillary pressure remained constant. Since there was an insignificant increase in the cardiac output in the first three cases, there was a consequent further increase in the pulmonary vascular resistance. In case 9 there was no net increase in the pulmonary vascular resistance since there was a considerable increase in the cardiac output. Frank congestive heart failure was present in subjects 11 and 12. Although the pulmonary pressure gradient increased during hypoxia in these two subjects, there was a substantial increase in the pulmonary capillary pressure associated with a rise in the systemic arterial pressure, suggestive of an aggravation of left ventricular failure. In patient 10, who had isolated mitral stenosis, there was a tremendous rise in the pulmonary vascular resistance and a considerable decrease in the pulmonary capillary pressure during hypoxia, due perhaps to a transient sharp reduction in the volume of blood in the lungs. The other four subjects (cases 2, 4, 5, 6) showed no change in the

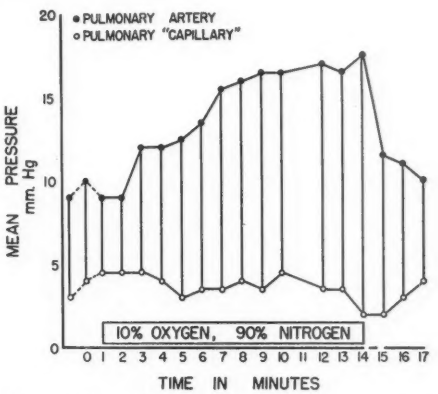

Fig. 1. Simultaneous registration of pulmonary arterial and pulmonary capillary pressures before, during and after inhalation of 10 per cent oxygen mixture.

TABLE 2—*Circulatory Responses to Hypoxia of Twelve Individuals with Cardiopulmonary Abnormalities*

Patient	Age	Surface Area	Remarks	Hematocrit Reading	Pulse Rate	Pulmonary Arterial Pressure			Pulmonary Capillary Pressure	Pulmonary Pressure Gradient	Systemic Blood Pressure			Arterial Oxygen Saturation	Mean Circulation Time	Oxygen Consumption	Arteriovenous Oxygen Difference	Cardiac Index		Stroke Volume	General Blood Volume	Pulmonary Blood Volume	PBV/GBV	Pulmonary Resistance	Right Ventricular Work	Total Peripheral Resistance	Left Ventricular Work
						Systolic	Diastolic	Mean			Systolic	Diastolic	Mean					Fick	Dye									
	(years)	(sq.M.)			(beats/min.)	(mm.Hg)			(mm. Hg)	(mm. Hg)	(mm.Hg)			(%)	(sec.)	(cc./sq. M./ min.)	(cc./ 100 cc.)	(L./ min./ sq.M.)		(cc.)	(cc./ sq.M.)	(cc./ sq.M.)	(%)	(dynes sec./ cm.^{5})	(Kg. M./ min./ sq.M.)	(dynes sec./ cm.^{5})	(Kg.M./ min./ sq.M.)
1 Chronic lung dis.	28	1.29	Control	45.9	120	25	12	19.0	4.5	14.5	115	75	92	75	8.9	150	4.4	3.3	3.6	38	2720	530	19	253	0.98	1572	4.8
			Hypoxia 13 min.	45.9	125	28	17	23.0	1.5	21.5	112	75	92	65	8.7	—	—	—	4.0	42	—	580	21	333	1.32	1412	5.3
2. Lung abscess	50	1.70	Control	28.3	100	21	9	16.0	1.5	14.5	105	60	70	94	10.2	132	4.7	2.8	4.5	77	2550	770	30	151	1.02	733	4.5
			Hypoxia 12 min.	28.7	115	26	9	15.0	0.0	15.0	97	60	70	79	8.2	—	—	—	4.7	70	2580	640	25	151	0.83	706	4.8
3. Thyrotoxicosis	64	1.57	Control	39.2	94	38	6	17.0	4.0	13.0	155	62	89	95	8.9	187	2.8	6.6	4.8	80	3120	720	23	173	1.38	932	6.1
			Hypoxia 12 min.	39.4	107	60	15	31.0	5.0	26.0	180	75	115	81	9.3	—	—	—	5.0	72	2930	780	27	266	2.23	1159	8.3
4. Smoke inhalation	31	1.78	Control	43.7	90	18	7	11.0	1.0	10.0	115	75	90	92	13.0	158	4.8	3.3	3.0	62	3120	650	21	147	0.32	1358	3.9
			Hypoxia 14 min.	43.6	90	19	7	10.0	1.0	9.0	123	77	105	79	11.0	—	—	—	2.8	56	2930	520	18	147	1.80	1732	4.3
5. Es. hypertension	40	1.58	Control	39.4	95	14	5	9.0	1.0	8.0	175	110	127	91	9.6	113	4.2	2.7	2.8	47	2680	460	17	143	0.32	2082	5.1
			Hypoxia 18 min.	39.2	100	14	5	10.0	1.0	9.0	160	117	138	77	10.1	—	—	—	3.0	48	2880	510	18	151	0.38	2304	6.0
6. Diabetes; anemia	38	1.67	Control	31.3	90	18	6	10.0	1.0	9.0	118	65	82	90	9.5	126	4.0	3.1	3.1	57	2150	480	22	147	0.45	1279	3.6
			Hypoxia 11 min.	30.5	110	24	10	15.0	2.0	13.0	115	60	78	55	7.4	—	—	—	4.7	71	2070	580	28	133	1.01	799	5.3
7. Encephalitis	24	1.94	Control	45.5	100	12	3	8.5	1.5	7.0	100	65	75	92	12.1	135	6.1	2.2	2.6	51	2770	530	19	109	0.32	1172	2.8
			Hypoxia 9½ min.	45.9	105	19	9	14.0	2.5	11.5	85	48	60	63	12.9	—	—	—	2.5	46	2670	530	20	192	0.50	999	2.1
8. Chronic lung dis.	63	1.41	Control	47.7	95	80	37	45.0	10.0	35.0	140	80	112	69	—	189	4.6	4.1	—	61	3200	—	—	(480)	(2.06)	(1545)	6.6
			Hyperoxia 13 min.	47.2	95	85	32	48.0	10.0	38.0	155	80	110	100	11.0	—	—	—	4.0	60	3320	740	22	533	2.18	1545	6.3
			Hypoxia 8½ min.	49.5	105	95	60	65.0	10.0	55.0	165	90	122	47	10.9	—	—	—	4.3	58	—	790	24	719	3.40	1598	7.2
9. Chronic lung dis.	50	1.58	Control	32.7	90	42	14	24.0	5.0	19.0	175	90	120	83	12.1	163	3.9	4.2	3.5	62	2690	720	27	266	0.95	1718	6.0
			Hypoxia 11½ min.	33.5	100	50	18	29.0	5.0	24.0	172	90	123	63	10.2	—	3.4	—	4.7	75	2790	810	29	253	1.62	1305	8.3
10. Mitral stenosis	23	1.48	Control	39.0	98	95	33	66.0	32.0	34.0	118	75	92	97	19.7	148	6.7	2.2	2.3	35	2750	750	27	786	2.15	2224	3.1
			Hypoxia 8 min.	39.8	145	130	70	92.0	15.0	77.0	120	70	83	72	14.2	—	—	—	2.4	24	—	560	20	2105	3.17	1891	2.9
11. Mitral stenosis; CHF	51	1.84	Control	44.4	±86	62	27	40.0	22.0	18.0	145	80	95	94	15.7	135	7.7	1.7	2.1	44	3450	540	16	386	1.20	1998	2.8
			Hypoxia 10 min.	45.8	+110	85	45	58.0	30.0	28.0	150	80	110	74	17.9	—	—	—	1.9	32	—	570	17	639	1.60	2531	3.0
12. Acute nephritis	45	1.98	Control	30.3	80	43	14	28.0	18.0	10.0	183	98	132	89	11.3	150	4.2	3.6	4.0	100	3140	760	24	100	1.61	1319	7.6
			Hypoxia 11 min.	31.6	100			38.0	25.0	13.0	180	100	140	72	9.7	—	—	—	5.6	110	—	900	29	95	3.05	1026	11.2

pulmonary vascular resistance and in only one (case 6) was there a significant increase in the cardiac output. The changes in the pulmonary blood volume in this group appear to have been random. The tendency for the "pulmonary blood volume" to be larger than in the normal group may have been associated with a large left ventricle.

Discussion

The production of pulmonary hypertension in our normal subjects by short periods of hypoxia agrees with previously reported studies in animals[10, 11] and in man.[1] Insofar as we are aware it has not hitherto been reported that hypoxia does not affect the pulmonary capillary pressure in man. It is of interest that Liljestrand[10, 11] has found that the left atrial pressure in the cat is unaltered by hypoxia. It is now generally agreed that both in animals and in man the pulmonary capillary, the pulmonary venous, the left atrial and the left ventricular end diastolic pressures are of approximately the same magnitude.

The pulmonary pressor response to hypoxia is of rapid onset, as is shown by our studies and by the observations of Motley[1] and of Liljestrand.[10, 11] In this respect the observations of Dirken and Heemstra[12, 13] are difficult to interpret. These workers found only a very gradual reduction in blood flow through the unilaterally hypoxic rabbit lung, but no data are given concerning changes in the vascular pressures or the vascular resistance in that organ.

The cardiac output in the normal individual is shown in our study to be increased by hypoxia. This is in agreement with observations in animals[14] and in man.[15, 16] The slight reduction in the cardiac output in normal man during hypoxia reported by Motley[1] was due to an apparently reduced oxygen consumption. At an altitude of 20,000 feet a period of 50 to 60 minutes is required for the alveolar respiratory quotient to return to the control value.[17] An approximately equivalent time would presumably be required during the inhalation of 10 per cent oxygen. Subsequent observations in Cournand's laboratory have shown that the cardiac output normally increases during hypoxia.[18] The dye dilution technic for determining the cardiac output obviates the problem of achieving a steady state. A fair correlation exists between the intensity of the hypoxia and the increase in the cardiac output in the normal group. Since the systemic blood pressure either is unchanged or declines slightly, the increase in the cardiac output is presumably initiated by the fall in the total peripheral vascular resistance. This increase in the blood flow is the primary compensatory mechanism whereby oxygen transport to the tissues is maintained during hypoxia.[14, 16]

The mechanism of the pulmonary hypertension and of the increase in the pulmonary vascular resistance during hypoxia is not entirely clear. Under our experimental conditions it cannot be explained by the moderate increase in the cardiac output. The absence of a rise in the pulmonary capillary pressure excludes a "back-pressure" effect from the left heart. It has recently been suggested that an increased flow through the bronchial arteries may account for the pulmonary hypertension of hypoxia.[19] Such an occurrence during an acute experiment seems also to be excluded by the failure of the pulmonary capillary pressure to rise during hypoxia, and by the collateral evidence that in the dog the bronchial arterial flow represents less than 1 per cent of the cardiac output.[20] It appears unlikely that the lymphatic drainage from the lungs is significantly impeded by a short period of hypoxia. As pointed out by Motley,[1] respiratory alkalosis cannot account for the pulmonary pressor response; furthermore, where measured in our cases, the changes in arterial and venous carbon dioxide tension and hydrogen ion concentration were not large. The remaining possibility, then, is that acute hypoxia causes a constriction of the pulmonary precapillary vessels. It has been concluded by Liljestrand[11] and by Dirken and Heemstra[21] that the most likely mechanism of this vasoconstriction is a direct effect of the low oxygen tension of the returning venous blood on the walls of the pulmonary arterioles. Figure 2 illustrates rapidly consecutive oximetric observations during induced hypoxia on the systemic arterial and on the right ventricular blood with a simultaneous

continuous pressure recording from the pulmonary artery. There is some suggestion that the pressure changes coincide with the changes in oxygen tension of the venous blood more closely than with those of the arterial blood. The point is difficult to prove. While the results of Dirken and Heemstra[12, 13, 21] do not correspond with observations in man, under their experimental conditions they cannot attribute hypoxic pulmonary hypertension to autonomic nervous activity, to changes in carbon dioxide tension, to epinephrine, ergotamine, acetylcholine and physostigmine or histamine.

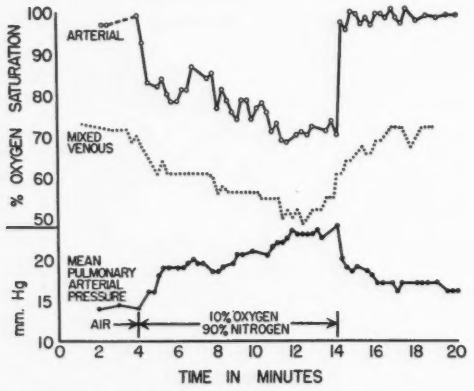

FIG. 2. Rapidly consecutive oximetric observations of oxygen saturation of heat-flushed ear and of blood aspirated from right ventricle correlated with continuous recording of pulmonary arterial mean pressure before, during and after inhalation of 10 per cent oxygen mixture.

This diffuse pulmonary vasoconstriction produced in normal individuals by experimental hypoxia is of no obvious value. In lung disease, on the other hand, as pointed out by Liljestrand,[11] segmental pulmonary arteriolar constriction in response to a local reduction in oxygen tension should be a useful protective mechanism. By this means arterial oxygen saturation could be maintained by the deflection of the pulmonary arterial stream away from poorly aerated toward better aerated lung tissue.

The circulatory responses to hypoxia of the abnormal subjects follow no pattern. In general, those with a pre-existent pulmonary hypertension showed a further rise in pressure during hypoxia, although with a few exceptions the increase in the pulmonary pressure gradient was not so striking as in the normal group. In some individuals, for no obvious reason, there was no pulmonary pressor response to hypoxia. In only two instances was there a significant increase in the cardiac output. As a rule the increase in the pulmonary vascular resistance was relatively lower than in the normal group. As a corollary of the slight change in the cardiac output, the peripheral vascular resistance tended to increase. While there were suggestive differences in some cases, no indisputably significant relocation of the pulmonary blood volume could be demonstrated.

It would appear that individuals with cardiopulmonary abnormalities are particularly vulnerable to hypoxia for two reasons. First, they may be unable to respond to local pulmonary disorders with effective pulmonary arteriolar constriction. Second, they are unable to maintain oxygen transport to the tissues by increasing cardiac output. This was apparent from the severity of the dyspnea caused by the experimental procedure. From the clinical standpoint these people are seriously jeopardized by the respiratory stresses of pulmonary embolization, atelectasis, pulmonary infection, heavy sedation, acute blood loss, high altitude and so forth. Thus, they can neither maintain arterial oxygen saturation by reducing blood flow through airless or poorly aerated lung nor compensate by increasing peripheral blood flow.

The observations reported here demonstrate that the pulmonary arteriocapillary pressure gradient can be strikingly increased without significant alterations in the pulmonary blood volume or the blood flow indicating a pulmonary vasoconstrictive mechanism. On the other hand, by the abrupt expansion of the blood volume without necessarily increasing the blood flow, a considerable increase in both the pulmonary arterial and the pulmonary capillary pressures can be produced without altering the pulmonary arteriocapillary pressure gradient.[23] Under these circumstances the pulmonary vasculature apparently behaves as an elastic reservoir. With our present technics,

by neither maneuver is it possible to demonstrate a significant alteration in the pulmonary blood volume in relation to the general blood volume. It is apparent that pulmonary abnormalities in patients with heart disease represent a complex interrelationship between impaired myocardial function, pressure-volume factors, pulmonary vascular disease, vasomotor activity, impaired lymphatic drainage and other factors still unrecognized.

Summary and Conclusions

The acute circulatory reactions to short periods of hypoxia have been studied in eight normal individuals and in 12 individuals with cardiopulmonary dysfunction.

In the normal group, a rapid reduction in the arterial oxygen saturation to about 75 per cent caused a considerable increase in the pulmonary vascular resistance and in the cardiac output. The pulmonary capillary pressure was not altered.

In the abnormal group, a similar reduction in the arterial oxygen saturation caused a much smaller increase in the pulmonary vascular resistance and little or no increase in the cardiac output. The pulmonary capillary pressure was not altered. A few exceptions to this were noted. In contrast with the normal group, the inhalation of the low oxygen mixture caused severe dyspnea.

The most probable cause of the increase in the pulmonary arterial pressure during hypoxia is a direct effect of the low oxygen tension of the returning venous blood on the walls of the pulmonary arterioles. The increase in the cardiac output is a compensatory reaction, initiated by a fall in the peripheral vascular resistance, whereby oxygen transport to the tissues is maintained. In pulmonary disease these reactions may serve a useful purpose. In the presence of severe cardiopulmonary disease these reactions are impaired.

Definite evidence of alterations of the pulmonary blood volume during hypoxia could be demonstrated in neither the normal nor the abnormal group.

Acknowledgment

This work was carried out with the technical assistance of Misses Eloise Cavin, Elizabeth Kelly, Mary Upshaw, Ann Payne and Mary McPhaul.

References

[1] Motley, H. L., Cournand, A., Werko, L., Himmelstein, A., and Dresdale, D.: The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. Am. J. Physiol. **150:** 315, 1947.

[2] Warren, J. V.: Determination of cardiac output in man by right heart catheterization. In Potter, V. R.: Methods in Medical Research, Vol. I. Chicago, Yearbook Publishers, 1945.

[3] Hellems, H. R., Hayes, F. W., and Dexter, L.: Pulmonary "capillary" pressure in man. J. Appl. Physiol. **2:** 24, 1949.

[4] Van Slyke, D. D., and Neill, J. M: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61:** 523, 1924.

[5] Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Vol. II, Methods. Baltimore, Williams and Wilkins, 1932.

[6] Stewart, G. N.: The output of the heart in dogs. Am. J. Physiol. **57:** 27, 1921.

[7] Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the circulation. IV. Further analysis of the injection method and of changes in hemodynamics under physiological and pathological conditions. Am. J. Physiol. **99:** 534, 1932.

[8] Ebert, R. V., Borden, C. W., Wells, H. S. and Wilson, R. H.: Studies of the pulmonary circulation. I. The circulation time from the pulmonary artery to the femoral artery and the quantity of blood in the lungs in normal individuals. J. Clin. Investigation **28:** 1134. 1949.

[9] Dexter, L., Dow, J. W., Haynes, F. W., Whittenberger, J. L., Ferris, R. G., Goodale, W. T., and Hellems, H. R.: Studies of the pulmonary circulation at rest. Normal variations and the interrelations between increased pulmonary blood flow, elevated pulmonary arterial pressure and high pulmonary "capillary" pressures. J. Clin. Investigation **29:** 602, 1950.

[10] Von Euler, U. S., and Liljestrand, G.: Observations on the pulmonary arterial blood pressure in the cat. Acta. Physiol. Scandinav. **12:** 301, 1946.

[11] Liljestrand, G.: Regulation of pulmonary arterial blood pressure. Arch. Int. Med. **81:** 162, 1948.

[12] Dirken, M. N. J., and Heemstra, H.: Alveolar oxygen tension and lung circulation. Quart. J. Exper. Physiol. **34:** 193, 1948.

[13] —, and —: The adaptation of the lung circulation to the ventilation. Quart. J. Exper. Physiol. **34:** 213, 1948.

[14] Harrison, T. R., and Blalock, A.: The regulation of circulation. VI. The effects of severe anoxemia of short duration on the cardiac output of morphinized dogs and trained unnarcotized dogs. Am. J. Physiol. **80:** 169, 1927.

[15] KEYS, A., STAPP, J. P., AND VIOLANTE, A.: Responses in size, output and efficiency of the human heart to acute alteration in the composition of inspired air. Am. J. Physiol. **138:** 763, 1943.

[16] STARR, I., AND MCMICHAEL, M.: Oxygen transport, circulation and respiration in healthy subjects at simulated altitudes of 16,000–18,000 feet. J. Appl. Physiol. **1:** 430, 1948.

[17] RAHN, H., AND OTIS, A. R.: Alveolar air during simulated flights to high altitudes. Am. J. Physiol. **150:** 202, 1947.

[18] FISHMAN, A., RILEY, R. L., AND COURNAND, A., cited by COURNAND, A.: Some aspects of the pulmonary circulation in normal man and in chronic cardiopulmonary diseases. Circulation **2:** 641, 1950.

[19] MCCANN, W. S.: Some neglected aspects of cardiology: circulatory function of the respiration. Am. J. Med. **8:** 62, 1950.

[20] BRUNER, H. D., AND SCHMIDT, C. F.: Blood flow in the bronchial artery of the anesthetized dog. Am. J. Physiol. **148:** 648, 1947.

[21] DIRKEN, M. N. J., AND HEEMSTRA, H.: Agents acting on the lung circulation. Quart. J. Exper. Physiol. **34:** 227, 1948.

[22] Unpublished data.

[23] DOYLE, J. T., WILSON, J. S., ESTES, E. H., AND WARREN, J. V.: The effect of intravenous infusions of physiologic saline solution on the pulmonary arterial and pulmonary capillary pressure in man. J. Clin. Investigation **30:** 345, 1951.

The Effects of Work on the Pulmonary Circulation in Mitral Stenosis

By HARALD ELIASCH, M.D., GEOFFREY WADE, M.B., M.R.C.P. AND LARS WERKÖ, M.D.

In an attempt to understand more fully the hemodynamic effects in mitral stenosis, the vascular response to effort was studied in 12 cases. It was found that pulmonary arterial pressures rose, but did not necessarily parallel changes in the pulmonary "capillary venous" pressure (pcv), suggesting that the response pattern may be modified by secondary pulmonary vascular change. Further, in some studies, pulmonary "capillary venous" pressures were found to rise initially and then fall despite continuing work, emphasizing the necessity to choose work of such a degree and duration that a steady state may be obtained.

IN 1946 Bloomfield and co-workers,[1] by passing a catheter into the pulmonary artery, demonstrated the presence of pulmonary hypertension in mitral stenosis, while Hickam and Cargill[2] in 1948 showed that this pressure rose on exercise. The ability to measure the pulmonary "capillary venous" pressure[3, 4] permitted a fuller understanding of the circulatory dynamics in mitral stenosis. The response to effort in patients with this condition is an important part of the clinicopathologic picture, and the purpose of this paper is to present changes in pressures and flow on graded work which occurred in 13 studies made on 12 cases of mitral stenosis.

MATERIAL

Patients were selected at random, and all had typical signs of mitral stenosis. No patient was in right heart failure at the time of the study. Functional grouping[5] and clinical data are summarized in table 1.

TECHNIC

All cases were studied in the morning, recumbent, and in the postabsorptive state. The pulmonary artery was catheterized.[1] The pulmonary "capillary venous" pressure (pcv) was recorded, using the technic described by Lagerlöf and Werkö.[3] An indwelling needle was placed in the brachial artery. All pressures were recorded with the Tybjaerg-Hansen and Warburg manometer, mean pressures being recorded by electrical filtration.[7] Cardiac output was determined by the direct Fick method. Total plasma volume was estimated with Evans blue dye.[8] The mean circulation time and cardiopulmonary blood volume were calculated.[9] Vascular resistances were calculated with the usual formulas.

All basal estimations were made following a period of 30 minutes rest. Work was then performed on a bicycle ergometer with the patient in supine position. Pressures were first recorded after the legs had been raised to the pedals but before work actually commenced. Work was performed over a period of 10 to 20 minutes and was of a degree well within the patients capabilities (approximately 70 Kg. per minute). Pressures were recorded at frequent intervals throughout the period of work. The catheter was left in the pulmonary capillaries as long as seven minutes and then withdrawn into the pulmonary artery. Cardiac output and cardiopulmonary blood volume by dye method were estimated two minutes before cessation of work. Work was not stopped for the purpose of pressure and flow estimations.

Further pressure recordings were made 5 to 15 minutes after cessation of work, in some cases in the pulmonary capillaries as well as in the pulmonary artery. Cardiac output by the Fick method was also estimated in most cases. Finally, on withdrawal, pressures were recorded in the right ventricle and the right auricle.

RESULTS

Cardiac Output. On commencing work the pulse rate invariably rose, an approximately constant rate being obtained after periods of one to four minutes.

The basal oxygen consumption ranged between 123 and 168 ml. per minute per square meter of surface area, rising on effort to between 187 and 286 ml. per minute per square

From the IVth Medical Service, St. Erik's Hospital, Stockholm, Sweden. The work described in this paper was aided by a grant from the Swedish Medical Research Council.

During the course of the work, one of us (G. W.) was Dickinson Fellow in Medicine, University of Manchester.

meter of surface area. The basal A-V oxygen difference did not exceed 5.5 volumes per hundred cc., at rest, but increased on effort to a pathologic extent in six studies (greater than 6.8 volumes per 100 cc. at an oxygen consumption less than 400 ml. per minute per square meter of surface area[2]).

The resting cardiac indexes were from 2.5 to 4.7 liters per minute, rising on effort in seven studies and not changing significantly in six. In three of these latter studies the A-V oxygen difference remained within normal limits.

Pulmonary Pressures. In studies Nos. 311 and 331 the pulmonary "capillary venous" pressure was within normal limits, both at rest and on effort. In the other studies the resting pulmonary "capillary venous" pressure was abnormally high, ranging between 13 and 25 mm. Hg. The response to effort was of three types: (a) In studies Nos. 306a, 315 and 316 an initially high pulmonary "capillary venous" pressure (25, 23 and 25 mm. Hg, respectively) did not increase further. (b) In studies Nos. 321, 324, 337 and 338 a moderately increased pulmonary "capillary venous" pressure (14, 18, 19 and 16 mm. Hg, respectively) rose further on effort, remaining at a constant level throughout the duration of work. (c) In studies Nos. 320, 322, 332 and 334 a moderately elevated resting pulmonary "capillary venous" pressure (13, 14, 19 and 21 mm. Hg, respectively) rose sharply after two to three minutes work, falling again to a level which was constant during the remaining period of work. In two of these studies it fell back to the basal value, but was above this level in the other two (figs. 1 and 2).

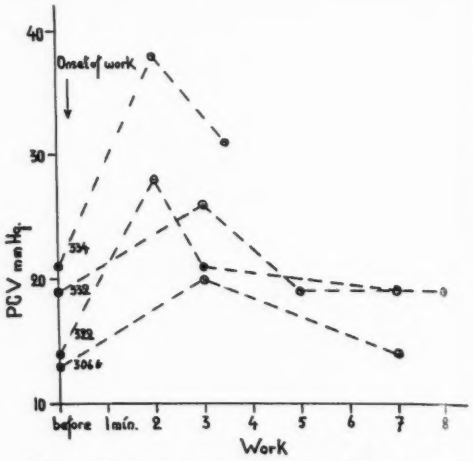

FIG. 1. Changes in pulmonary "capillary venous" pressure on work in four cases of mitral stenosis.

TABLE 1.—*Summary of Clinical Data*

	Case No.												
	306a	306b	311	315	316	321	322	324	331	332	334	337	338
Sex	F	F	F	F	M	F	M	F	M	F	F	F	F
Age	41	41	32	39	38	32	29	33	43	26	39	44	34
Functional grouping	III	II	II	III	III	II	III	II-III	II-III	II	III-IV	II-III	II
Heart vol.[6] ml./M.[2]	565	570	425	545	500	680	550	565	510	500	480	470	370
Remarks	Before commissurotomy	After commissurotomy	Pregn. III month	—	—	After commissurotomy	—	Fibrillation	After commissurotomy	—	—	—	Pregn. IV month

The resting pulmonary arterial pressures (PA) were within normal limits in only one study (No. 311), and there was no significant rise on effort. In all other studies there were varying degrees of pulmonary hypertension at rest, the pressures increasing further on effort. This increase affected the systolic more than the diastolic pressures with a consequent increase in pulse pressure in all but one study.

Pulmonary Pressure Gradient. Figure 3 shows graphically the changes in pulmonary arterial mean–pulmonary "capillary venous" pressure gradient occurring on effort. In four cases with a basal pulmonary "capillary venous" pressure below 20 mm. Hg the gradient did not change significantly. In the remaining cases the mean pulmonary arterial pressures rose more than the pulmonary "capillary venous" pressures. This increase in gradient tended to

TABLE 2.—*Pressures and Flow at Rest, on Effort and on Recovery*

Case No.	State	Pulse rate	Oxygen consumption ml./M.²	A-V O_2 diff. ml./Liter	Cardiac index	Pulmonary arterial pressure			PCV mean	Brachial arterial pressure			Pulmonary Resistance (dynes sec. cm.⁻⁵)	Cardiopulm. blood vol. (liters)	Cardiopulm. blood vol. (% of total blood vol.)
						S	D	M		S	D	M			
306a	B	78	145	55	2.6	87	41	58	25	123	80	93	678	—	—
	E	98	231	97	2.4	114	49	71	25	115	74	82	1050	—	—
	R	75	170	58	2.9	85	35	53	—	115	73	87	—	—	—
306b	B	71	134	44	3.1	44	19	30	13	132	84	103	309	1.07	26
	E	88	270	72	3.5	77	35	52	14	132	86	105	607	0.94	24
	R	77	150	54	2.7	40	16	27	12	121	81	98	308	—	—
311	B	73	151	32	4.5	21	11	15	10	112	67	77	51	1.10	17
	E	92	—	52	—	23	10	17	12	120	71	88	—	1.26	18
	R	81	165	43	3.9	19	7	12	9	117	75	89	38	—	—
315	B	100	168	52	3.4	39	18	28	23	124	82	98	78	0.91	21
	E	118	274	83	3.3	55	37	45	22	139	90	110	360	1.16	16
	R	94	—	56	—	37	15	25	—	113	78	92	—	—	—
316	B	78	143	51	2.8	63	29	41	25	134	89	108	251	1.29	20
	E	97	343	84	4.1	102	46	67	26	147	97	115	443	1.44	20
	R	81	173	59	2.9	65	27	40	21	133	85	102	281	—	—
321	B	78	140	46	3.0	36	15	24	14	136	76	97	160	0.88	16
	E	92	229	67	3.4	63	25	41	20	150	88	109	300	0.68	17
	R	80	134	53	2.9	33	16	24	9	133	73	93	255	—	—
322	B	100	167	53	3.3	39	12	21	14	96	68	80	84	1.66	24
	E	106	204	63	3.4	51	24	34	19	99	69	82	172	1.75	21
	R	100	164	53	3.1	43	14	22	—	102	72	81	—	—	—
324	B	76	131	53	2.5	29	16	21	18	113	77	91	61	1.04	28
	E	112	286	89	3.2	48	24	33	30	132	87	106	47	1.03	22
	R	80	—	61	—	26	11	17	15	—	—	—	—	—	—
331	B	67	162	42	3.9	33	11	20	10	123	78	96	116	1.57	19
	E	75	271	63	4.3	38	17	25	13	125	75	96	125	2.73	33
	R	67	—	39	—	30	11	19	—	130	87	105	—	—	—
332	B	91	123	32	3.8	33	17	22	19	121	78	92	41	1.16	24
	E	113	187	51	3.7	35	18	24	19	125	78	93	71	1.63	27
	R	89	—	—	—	25	10	15	—	115	74	87	—	—	—
334	B	72	126	50	2.5	46	25	32	21	128	85	104	220	0.84	15
	E	95	236	78	3.0	71	40	51	31	136	91	109	334	1.03	19
	R	81	143	56	2.6	44	18	30	22	128	89	106	157	—	—
337	B	76	127	46	2.8	33	15	21	19	129	77	100	35	1.29	26
	E	93	265	63	4.2	48	23	34	24	139	83	105	114	1.35	28
	R	72	127	49	2.6	28	12	17	11	118	71	89	111	—	—
338	B	95	128	32	3.9	29	17	21	16	118	75	94	59	1.38	20
	E	105	270	50	5.3	36	22	29	24	126	88	99	43	1.60	22
	R	81	129	31	4.2	30	17	21	18	112	66	81	34	—	—

B = Basal
E = Effort
R = Recovery
(Pressures in mm. Hg; referred to 5 cm. below the sternal notch.)

be greatest in those studies with a high resting pulmonary "capillary venous" pressure; in four studies a considerable rise in pulmonary arterial mean pressure occurred in the absence of a rise in pulmonary "capillary venous" pressure.

Cardiopulmonary Blood Volume. Under basal conditions the cardiopulmonary blood volume was within normal limits in all studies. In only two studies was there a significant change

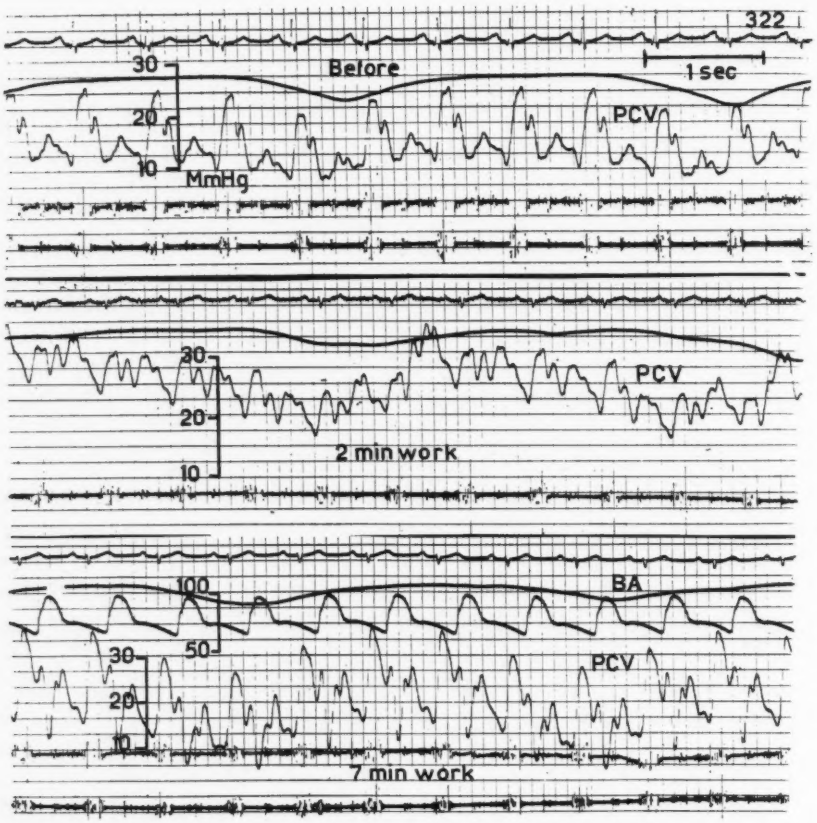

FIG. 2. Simultaneous recording of pulmonary "capillary venous" pressure, respiration, electrocardiogram and phonocardiogram at rest, after two minutes' work and after seven minutes' work. In the third tracing brachial arterial pressure is also recorded.

Pulmonary Resistance. The pulmonary arteriolar resistance varied widely in different studies. In Nos. 311, 331, 332 and 338 the resting values were within normal limits and did not rise on effort. In the remaining studies the basal values ranged between 84 and 678 units and up to 1050 units on effort. The changes in resistance paralleled the alteration in pulmonary arterial mean–pulmonary "capillary venous" pressure gradient, tending to be greatest in those with a high resting pulmonary "capillary venous" pressure.

Cardiopulmonary Blood Volume. Under basal conditions the cardiopulmonary blood volume was within normal limits in all studies. In only two studies was there a significant change on effort (Nos. 331 and 332), both showing an increase.

Systemic Circulation. The changes observed in the systemic circuit were small. A slight rise in arterial pressure occurred in six studies; there was no change in six, and in one study there was a slight fall.

Recovery. On recovery flow and pressure approximated the basal values in most studies. In No. 321 (fig. 4) and No. 337 the pulmonary

"capillary venous" pressure fell considerably below the basal value, and this was accompanied in No. 337 by a fall in the pulmonary arterial pressures, although the pulmonary arterial mean–pulmonary "capillary venous" pressure gradient was increased. Abnormally low pulmonary arterial pressure values on recovery were also observed in study No. 332, but a simultaneous pulmonary "capillary venous" recording was not available. In the latter studies there was no significant change in cardiac output.

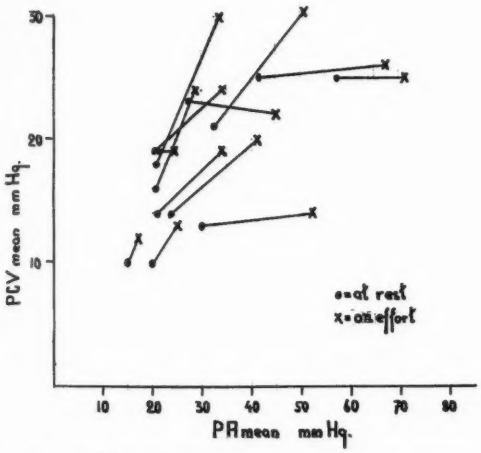

FIG. 3. The relation between pulmonary "capillary venous" mean and pulmonary arterial pressure at rest and on effort. Closed circles = at rest, × = on effort.

DISCUSSION

The correct assessment of the circulatory response to effort depends on the work being of such a degree and duration that a steady state can be achieved. This is fundamental, for unless a steady state is achieved, not only is the direct Fick method, and consequently all calculations involving the cardiac output, invalid, but the pattern of pressure response may also be changing. For this reason light work for a period of 10 to 20 minutes was adopted. That a steady state was probably achieved was shown by a constant pulse rate and steady pressures after the fifth minute of work in all studies. Further, estimations of oxygen consumption and cardiac output after the fourteenth and eighteenth minute of work in two studies showed no significant change.

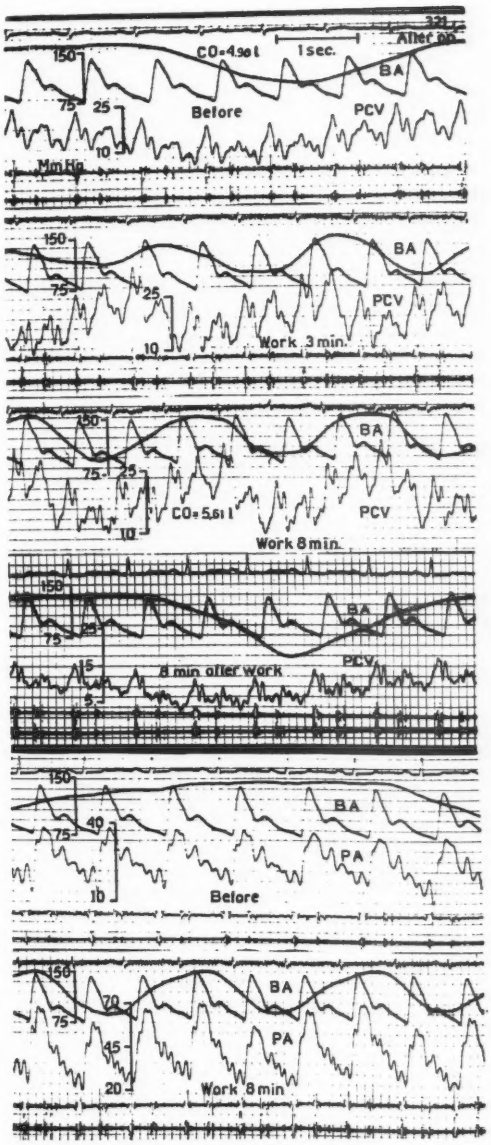

FIG. 4. Simultaneous recordings of pressure in the pulmonary capillaries, pulmonary and brachial arteries together with respiration, electrocardiogram and phonocardiogram at rest, on effort and after recovery.

It is also desirable that the resting figures should be obtained under basal conditions.

Despite all precautions the pulse rate was high and the arteriovenous oxygen difference low in studies Nos. 332 and 338. Finally, it is preferable not to use morphine-containing drugs in premedication, since they may themselves be a cause of pulmonary hypertension.[10]

The limited rise in flow on effort in advanced cases of mitral stenosis was pointed out by Meakins and co-workers in 1923.[11] In seven of the present studies the rise was inadequate, as shown by an abnormally great arteriovenous oxygen difference in relation to the oxygen consumption. In study No. 332 an unchanged cardiac output was accompanied by a normal arteriovenous oxygen difference of 5.1 volumes per 100 cc. As the resting figures in this study were probably not obtained under basal conditions, this response was not necessarily abnormal.

Although there is considerable evidence showing that in normal subjects and in patients with auricular septal defects the pulmonary "capillary venous" pressure is a good index of left auricular pressure,[3, 4, 12-14] the relationship may not be maintained in mitral stenosis. The pathologic changes known to occur in the lungs in mitral valvular disease[15-17] must play a part in conditioning the pattern of the pulmonary "capillary venous" pressure response to effort by disturbing pressure-volume relationships. The increased degree of dyspnea proportional to the amount of effort with possible changes in the intrapleural pressures may also be concerned.

In two studies the response to effort was normal, the pulmonary "capillary venous" pressure rising only to 12 and 13 mm. Hg, respectively. Presumably in these cases there was no significant rise in left auricular pressure, and the pressure-volume relationships of the pulmonary capillary bed were not abnormal at the level of the output. In five studies the pulmonary "capillary venous" pressure rose promptly and remained elevated. It is possible that this was due to a corresponding rise of the left auricular pressure, but doubt is cast on this explanation by the behavior of the pulmonary "capillary venous" pressure in the four studies shown in figure 1. It is possible that transitory imbalance between right and left ventricular outputs is responsible for the early rise and later fall in pulmonary "capillary venous" pressure, but some increase in the distensibility of the lung following a period of increased congestion cannot be excluded.[18] Slowly developing arteriolar vasoconstriction may also be possible, for although the existence of active vasomotor mechanisms is by no means certain,[19-21] recent studies suggest that they may occur.[22-24] Other factors to be considered are a slow redistribution of blood in the lungs, the development of right ventricular failure and an excessively short diastolic filling time. It is unlikely that these two latter factors were concerned in the reported studies. All patients were ambulant and had shown no signs of peripheral congestion at work levels higher than those of the study. Also, if failure had developed in the course of the study, it is unlikely that a steady state would have been achieved. A shortened diastolic filling time played no part, for the heart rate was not more rapid during the first three minutes of work than it was later.

Uncertain though the factors underlying changes in pulmonary "capillary venous" pressure are, the results emphasize the necessity to maintain effort for a period longer than four to five minutes.

In two studies there was a significant rise in cardiac output without any change in pulmonary "capillary venous" pressure, a finding at variance with results reported by other workers.[25] The explanation may lie in the fact that these workers used greater loads and recorded pressures and flow after only two to three minutes work. Under these circumstances a steady state could not have been achieved. Further, these workers recorded pressures and flow during different three minute work periods, which were separated by an interval of rest. Results obtained in this laboratory (not reported in this study) suggest that under these conditions, there may not be a similar vascular response pattern at the same work and output levels.

With the exception of one study, in which all pulmonary pressures were normal throughout, there was a varying degree of resting pulmonary hypertension increasing further on ef-

fort. In two studies rises of 8 and 12 mm. Hg in the pulmonary capillaries were accompanied by a parallel rise in pulmonary arterial mean pressure and a fall in pulmonary arteriolar resistance. In four studies a large increase in pulmonary arterial pressures occurred in the absence of any change of pulmonary "capillary venous" pressure, the resistance rising considerably. In the remaining studies there was a varying rise in pulmonary mean arterial pressure and always an increase in resistance.

Although there is a good correlation between the resting pulmonary "capillary venous" pressure and the degree of pulmonary arterial pressure rise on effort (fig. 3), this rise could not itself be dependent on the rise in pulmonary "capillary venous" pressure alone, for this may remain constant, and the highest pulmonary "capillary venous" pressure levels were recorded in studies where only a moderate rise in pulmonary arterial pressure was observed. The secondary pathologic changes known to occur in mitral valvular disease cause a great reduction in the diameter of the arterioles and probably also an increase in the elasticity modulus. In such a system small changes in blood volume may cause large changes in pressure, and there need be no change in pulmonary "capillary venous" pressure. Such changes in volume may be too small to be detected by the available methods of estimating cardiopulmonary blood volume.

In these reported studies all gradations of response of the pulmonary arterial pressures to effort are seen, and generalizations on changes in pulmonary arteriolar resistance would seem to be unjustified. That the greatest pulmonary arterial pressure rise should be seen in those studies with a high resting pulmonary "capillary venous" pressure is to be expected, for pathologic change in the pulmonary vessels are most probably secondary to increases in the pulmonary venous pressure.

It is possible that in certain cases of mitral stenosis, where the secondary pulmonary vascular changes are extreme, the limited ability of the cardiac output to rise on effort may not be directly dependent on the orifice of the mitral valve, but rather on the degree of pulmonary arteriolar narrowing.

Summary

1. The vascular response to graded work was studied on 13 occasions in 12 cases of mitral stenosis.

2. The degree and duration of work was such that a steady state was obtained. The importance of this is discussed.

3. The cardiac output rose significantly in seven studies and remained unchanged in six. In four of these studies in which it rose, the rise was inadequate to meet the tissue demands as judged by the arteriovenous oxygen difference.

4. Pulmonary "capillary venous" pressures remained within normal limits in two studies. In the remaining studies the changes fell into three groups: (a) a high resting pulmonary "capillary venous" pressure rose no further on effort; (b) a moderately high resting pulmonary "capillary venous" pressure rose during the initial two to three minutes of work, and remained at this level until work was stopped; (c) following an initial rise the pulmonary "capillary venous" pressure fell again after two to four minutes and remained constant thereafter.

5. Resting pulmonary pressures were high in all but one study. On effort pressure rose further, but this rise was not necessarily dependent on a rise in pulmonary "capillary venous" pressure.

6. In some studies the pulmonary arteriolar resistance remained normal; in others it was greatly increased. Those cases in which the increase in resistance on work was greatest showed no change in pulmonary "capillary venous" pressure.

7. The significance of these results is discussed in relation to the pathologic changes known to occur in the pulmonary vessels and also to changes in the cardiopulmonary blood volume. It is suggested that secondary vascular changes play a large part in conditioning the pattern of the response to effort.

Acknowledgments

The authors are indebted to Miss E. Ekberg, Mrs. B. Ekdahl and Miss M. Hansson for their technical assistance, and to Dr. B. Wehle for his help with the dye injection technic.

REFERENCES

[1] Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. S., and Richards, D. W., Jr.: Recording of right heart pressure in normal subjects and in patients with chronic pulmonary disease and various types of cardiocirculatory disease. J. Clin. Investigation **25:** 639, 1946.

[2] Hickam, J. B., and Cargill, W. H.: Effect of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. J. Clin. Investigation **27:** 10, 1948.

[3] Lagerlöf, H., and Werkö, L.: The pulmonary capillary venous pressure pulse in man. Scandinav. J. Clin. & Lab. Investigation **1:** 147, 1949.

[4] Hellems, H. K., Haynes, F. W., and Dexter, L.: Pulmonary "capillary" pressure in man. J. Applied Physiol. **2:** 24, 1949.

[5] Criteria for the Classification and Diagnosis of Heart Disease, ed. 4. New York, New York Tuberculosis and Health Association, 1940.

[6] Liljestrand, G., Lysholm, E., Nylin, G., and Zachrisson, C. G.: The normal heart volume in man. Am. Heart J. **17:** 406, 1939.

[7] Tybjaerg-Hansen, A.: Pressure measurements in the human organism. Teknisk Forlag, Copenhagen, 1949.

[8] Noble, R. F., and Gregersen, M.: Mixing time and disappearance rate of T-1824 in normal subjects and in patients in shock. Determination of plasma volume in man from 10-minutes sample. J. Clin. Investigation **25:** 158, 1946.

[9] Lagerlöf, H., Werkö, L., Bucht, H., and Holmgren, A.: Separate determination of the blood volume of the right and left heart and the lungs in man with the aid of the dye injection method. Scandinav. J. Clin. & Lab. Investigation **1:** 114, 1949.

[10] Unpublished Data.

[11] Meakins, J. C., D'Autrebande, L., and Fetter, W. J.: The influence of circulatory disturbances on the gaseous exchange of the blood. IV. The blood gases and circulation rate in cases of mitral stenosis. Heart **10:** 153, 1923.

[12] Calazel, T., Gerard, R., Daley, R., Draper, A., Foster, G., and Bing, R. J.: Comparison of right auricular, left auricular, the pulmonary capillary and pulmonary arterial pressures in cases of atrial septal defects. Bull. Johns Hopkins Hosp. **88:** 20, 1951.

[13] Werkö, L., and Lagerlöf, H.: The pulmonary capillary venous pressure in man. Communication to the First International Congress of Cardiology, Paris, 1950.

[14] Dow, J. W., and Gorlin, R.: Pulmonary capillary pressure as an index of left auricular mean pressure in dogs. Federation Proc. **9:** 33, 1950.

[15] Parker, F., Jr., and Weiss, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12:** 573, 1936.

[16] Larrabee, W. F., Parker, R. L., and Edwards, J. E.: Pathology of intrapulmonary arteries and arterioles in mitral stenosis. Proc. Staff Meet., Mayo Clin. **24:** 316, 1949.

[17] Edwards, J. E., and Burchell, H. B.: Multilobar pulmonary venous obstruction with pulmonary hypertension. Arch. Int. Med. **87:** 372, 1951.

[18] Mack, I., Grossman, J., and Katz, L. N.: The effects of pulmonary vascular congestion on the distensibility of the lungs. Am. J. Physiol. **150:** 654, 1947.

[19] Hamilton, W. F.: Pressure relations in the pulmonary circuit. Blood, Heart and Circulation. Washington, American Association for the Advancement of Science, 1940.

[20] Cournand, A.: Recent observations on the dynamics of the pulmonary circulation. Bull. New York Acad. Med. **23:** 27, 1947.

[21] Wiggers, C. J.: Physiology in Health and Disease. Philadelphia, Lea & Febiger, 1949.

[22] v. Euler, U., and Liljestrand, G.: Observations on the pulmonary arterial blood pressure in the cat. Acta Physiol. Scand. **12:** 301, 1946.

[23] Motley, H. L., Cournand, A., Werkö, L., Himmelstein, A., and Dresdale, D.: The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. Am. J. Physiol. **150:** 315, 1947.

[24] Eliasch, H., Werkö, L., and Lagerlöf, H.: Unpublished observations.

[25] Gorlin, R., Sawyer, C. G., Haynes, F. W., Goodale, W. T., and Dexter, L.: Effects of exercise on circulatory dynamics in mitral stenosis. III. Am. Heart J. **41:** 192, 1951.

Serum Cholinesterase Activity and Arterial Blood Pressure

By Louis J. Vorhaus, II, M.D.

Conflicting data have appeared in the literature regarding serum cholinesterase and blood pressure. The studies reported here were undertaken to establish or refute the existence of a direct relationship between these two factors. Two types of studies were performed. First, serum cholinesterase activity was measured in 63 unselected hypertensive patients. Second, a selected group of seven hypertensive patients and three healthy subjects was studied with a variety of drugs known to influence either blood pressure or serum cholinesterase. Results indicate that no direct relationship exists between blood pressure and serum cholinesterase and that fluctuations in these two factors occur independently of each other.

MANY investigators have speculated whether a direct relationship exists between the cholinesterase activity of the serum and the arterial blood pressure. Antipol, Tuchman, and Schifrin,[1] in 1937, first noted a tendency for patients with hypertension to have increased levels of serum cholinesterase activity. More recently, Farber[3] and Morelli[10] made similar observations in a small number of patients. The latter author suggested that essential hypertension might be due to an imbalance of the autonomic nervous system with sympathetic predominance, postulating that with increased circulating cholinesterase there would be abnormally great destruction of acetylcholine. On the other hand, Hall and Lucas[5] found no correlation between blood pressure levels and serum cholinesterse activity in 162 general hospital patients. Reichert and Frisch[12] made similar observations. Clinical and pharmacologic studies on the relationship of serum cholinesterase activity to various drugs have further confused the issue. Roepke[13] demonstrated that tetramethylammonium chloride, a drug closely related to tetraethylammonium chloride, inhibits serum cholinesterase activity in vitro. Schürtz[14] reported that prolonged barbiturate therapy caused a fall in serum cholinesterase activity both in guinea pigs and in man. Both of these drugs, when administered to hypertensive patients, generally mediate a fall in blood pressure. Torda and Wolff[15] observed in vitro that vitamin K (menadione) in concentration of 2×10^{-8} mols caused a 70 per cent decrease in serum cholinesterase activity, and Morelli and Salvi[11] observed that when vitamin K was given intravenously to hypertensive subjects it produced a drop both in serum cholinesterase activity and in blood pressure. On the other hand, Grob and coworkers[4] noted that diisopropyl fluorophosphate (DFP), a drug which irreversibly inhibits serum cholinesterase activity, when given to normotensive subjects, was without effect on the blood pressure, even when cholinesterase activity reached very low levels. It has also been observed that very high levels of serum cholinesterase activity occur in patients ill with the nephrotic syndrome,[4, 6, 17] and no hypertension is generally present in this condition. Davis and Hamilton[2] reported that folic acid, when given orally, increases the serum cholinesterase activity, and it is known that this drug does not mediate a rise in blood pressure.

The discrepancies in previous observations suggested the need for further investigation into the possible relationship between hypertension and serum cholinesterase activity. The studies reported here were undertaken in an attempt to establish or disprove the existence of such a relationship, to learn

From the Army Medical Nutrition Laboratory, Chicago, Ill., an Installation under the jurisdiction of the Office of the Surgeon General, U. S. Army, and the Department of Medicine, University of Illinois College of Medicine, Chicago, Ill.

The opinions expressed in this paper are those of the author and do not necessarily represent the official views of any governmental agency.

whether drugs known to influence serum cholinesterase activity have any effect on blood pressure, and to determine if any of a variety of drugs used in treatment of hypertension mediate their effects through inhibition of the enzyme.

Methods

Two types of observations were made. First, serum cholinesterase determinations were performed on 63 patients with essential hypertension, picked at random from the medical outpatient clinic of the Research and Educational Hospitals of the University of Illinois. Second, seven patients with essential hypertension were studied intensively on the research ward of the Research and Educational Hospitals. These were carefully chosen to include different types and grades of severity of hypertension. Data on the seven patients are summarized in table 1. Normotensive subjects studied as controls were all healthy adult male volunteers.

Thorough clinical examination was made on each patient and complete blood count, urinalysis, routine blood chemistry studies (including serology, fasting blood sugar, nonprotein nitrogen, and serum albumin and globulin), electrocardiograms, urea clearances, chest fluoroscopies and intravenous pyelograms were performed. Cholinesterase activity of the serum was determined by the electrometric method of Michel.[8, 9]

After a suitable control period, the following drugs were administered in sequence: vitamin K (as Hykinone), 20 to 72 mg. intravenously; folic acid, 15 to 90 mg. intravenously; sodium amytal, 180 mg. orally in three doses at hourly intervals; tetraethyl ammonium chloride, 3 cc. (300 mg.) intravenously; and diisopropyl fluorophosphate (DFP), 0.02 mg. per Kg. intramuscularly. Three patients were given cold pressor tests, two were treated with veratrum viride (Vertavis), one was given benzodioxane, 0.5 mg. intravenously, one was put on a rice diet for 17 days. As a control study, three normotensive subjects and four hypertensive patients were given sterile saline intravenously. During all of these studies frequent measurements of blood pressure and serum cholinesterase activity were performed. Results of the studies are tabulated in table 2.

Results

I. *Serum Cholinesterase Activity in Hypertensive Subjects*

The range of serum cholinesterase activity in 63 hypertensive patients was 0.61 Δ pH per hour to 1.42 Δ pH per hour, with a mean value of 0.90 Δ pH per hour and a standard deviation of 0.19 Δ pH per hour. These data compare favorably with those reported by Vorhaus and associates[16] for 68 healthy subjects, where the range was 0.68 Δ pH per hour to 1.37 Δ pH per hour, with a mean of 0.94 Δ pH per hour and a standard deviation of 0.16 Δ pH per hour. In the hypertensive patients there was no correlation between the level of blood pressure and the serum cholinesterase activity. Patients with malignant hypertension showed no higher levels of serum cholinesterase activity than those with benign hypertension.

Table 1.—*Patients Studied*

Patient	Age	Sex	Race	Type of Hypertension	Average Morning Blood Pressure	Known Duration of Disease
E. K.	36	Male	White	Malignant, advanced	230/130	3 years
M. C.	16	Female	White	Malignant, moderately advanced	200/120	6 months
J. C.	59	Female	White	Benign, severe	220/120	15 years
M. Q.	52	Female	White	Benign, mild	150/90	15 years
J. H.	40	Female	Negro	Malignant, early	190/100	1½ years
F. S.	67	Male	Japanese	Benign, mild	185/95	8 years
R. C.	43	Female	White	Benign, moderately severe	200/110	2 years

II. *Studies on Changes in Blood Pressure and Serum Cholinesterase Activity following Administration of Various Drugs*

A. *Sterile Saline.* As a control study, sterile saline was injected intravenously into three normotensive subjects and four hypertensive patients. In two cases (F. S. and W. T.) blood pressure recordings and serum cholinesterase determinations were performed in the manner described below with tetraethylammonium chloride. In the other five instances

the blood pressure recordings and serum cholinesterase determinations were performed in the manner described below with vitamin K. Insignificant changes in blood pressure and serum cholinesterase activity were noted following the administration of the saline and no correlation was observed between fluctuations in these two factors.

B *Vitamin K.* The vitamin was administered to three normotensive subjects and seven hypertensive patients. Blood pressure and serum cholinesterase activity were recorded every 15 minutes for the first hour and subsequently at half hour intervals up to four hours. In the hypertensive patients, mild drops in blood pressure were noted but there was no consistent period of time following administration of vitamin K when maximal effects occurred. No changes were noted in the normotensive subjects. All cases showed a significant drop in serum cholinesterase activity. No consistent correlation was observed in the fluctuations of blood pressure and serum cholinesterase activity, nor was any correlation observed between the magnitude of the fluctuations of either and the size of the dose of vitamin K administered.

C. *Folic Acid.* Folic acid was administered intravenously to five normotensive subjects and seven hypertensive subjects. For the most part, blood pressure and serum cholinesterase activity were recorded as with vitamin K. While mild drops in blood pressure were noted in all the hypertensive patients, mainly within the first two hours after administration of folic acid, the changes were not consistent and were not considered significant. Moderate but significant drops in serum cholinesterase activity occurred. However, no correlation was observed between the fluctuations of blood pressure and cholinesterase nor was there any observable correlation between the magnitude of these fluctuations and the size of the dose of folic acid administered.

TABLE 2.—*Changes in Blood Pressure and Serum Cholinesterase Activity following Administration of Drugs Tested*

Drug Administered	Number of Subjects Studied	Range of Maximal Blood Pressure Changes		Range of Maximal Changes in Serum Cholinesterase Activity	Mean Change in Serum Cholinesterase Activity
		Systolic	Diastolic		
		mm. Hg		%	%
Sterile Saline	7	Decrease 2 to 14	Decrease 2 to 10	+3 to −4	0
Vitamin K	10	Decrease 10 to 32	Decrease 10 to 22	−3 to −17	−11*
Folic Acid	12	Decrease 4 to 30	Decrease 0 to 12	0 to −20	−7*
Sodium Amytal	5	Decrease 18 to 62	Decrease 6 to 26	−2 to −5	−4*
Tetraethylammonium Chloride	7	Decrease 28 to 100	Decrease 10 to 48	−15 to −25	−19*
Diisopropyl Fluorophosphate	11	Decrease 0 to 38	Decrease 0 to 18	−37 to −94	−86*
Cold Pressor Test	3	Increase 22 to 50	Increase 12 to 36	+3 to −4	+1
Viratrum Viride	2	Decrease 30 to 150	Decrease 12 to 80	+3 to −2	+1
Benzodioxane	1	Increase 40	Increase 18	−4	−4
Rice Diet	1	Decrease 90	Decrease 30	+2	+2

* Change of statistical significance.

D. *Sodium Amytal.* Sodium amytal was administered to five hypertensive patients. Blood pressure recordings were made every half hour, and serum cholinesterase activity was determined every hour for six hours. In all cases mild to moderate drops in blood pressure occurred. Slight but statistically significant drops in serum cholinesterase activity were noted in each case. No correlation was observed between fluctuations in blood pressure and in serum cholinesterase activity.

E. *Tetraethylammonium Chloride.* Tetraethylammonium chloride was administered to seven hypertensive patients. Blood pressure recordings were made every half minute for the first 10 minutes, every minute for the next 10 minutes, every 5 minutes for the next 10 minutes, and then every 10 minutes for 30

minutes. Serum cholinesterase activity was estimated every minute for 10 minutes and subsequently with each blood pressure recording. All patients had moderate to profound fall in blood pressure which occurred during the first three minutes following administration of the drug. In every case the serum cholinesterase activity was observed to decrease significantly. In most cases the fall in blood pressure preceded the fall in serum cholinesterase activity, and the changes in these factors did not produce curves which were parallel or similar in shape. No correlation was noted between the magnitude of the fall in the blood pressure and in the serum cholinesterase activity; in fact the patient who had the greatest drop in blood pressure exhibited the smallest drop in cholinesterase.

F. *Diisopropyl Fluorophosphate* (*DFP*). This substance, in oil, was administered intramuscularly to four normotensive individuals and seven hypertensive patients. Two of the hypertensive patients (E. K. and J. H.) were subsequently given repeated injections every other day for six days, and one (E.K.) was subsequently given weekly injections for three weeks. Blood pressure recordings were made at thirty minute intervals for three hours, then hourly up to eight hours, then daily thereafter. Serum cholinesterase determinations were made at intervals of one, three, and six hours after injection of diisopropyl fluorophosphate and then daily for six days. Diisopropyl fluorophosphate, a drug which irreversibly inhibits cholinesterase,[7] produced the expected marked drop in serum cholinesterase activity in three to six hours, with a subsequent slow rise during the ensuing days as new serum cholinesterase protein was synthesized, in the manner already described by several investigators.[4, 6, 18, 19] In one case (F.S.) the drug administered came from an impotent lot, and only a small drop in serum cholinesterase activity occurred. In most cases, variable and insignificant drops in blood pressure occurred one to one and one-half hours after the injection, and in most cases the blood pressure returned to pre-injection levels while the serum cholinesterase depression remained marked. Multiple injections of diisopropyl fluorophosphate were without effect on blood pressure. In the patient who received an injection of impotent diisopropyl fluorophosphate the drop in blood pressure one and three-quarter hours later was as great as any in the group who had received the potent preparation.

G. *Cold Pressor Tests.* Three hypertensive patients were subjected to cold pressor tests, the right hand being immersed in ice water for one minute. Blood pressure was recorded every one-half minute for five minutes, and every minute thereafter for another five minutes. The serum cholinesterase activity was measured every minute for 10 minutes. In each case there was an abrupt rise in blood pressure during the first minute, with subsequent rapid fall to pre-test levels. Changes in serum cholinesterase activity were minimal and insignificant.

H. *Veratrum Viride.* Veratrum viride was administered to two patients. Patient M.C. received the drug for four days in amounts of 40 Craw units daily. This produced a mild drop in her blood pressure. No significant changes were noted in her serum cholinesterase activity. The second patient, E.K., received 40 to 100 Craw units daily for five days. No significant effect was observed in the blood pressure until early in the morning of the sixth day, when it suddenly dropped to 80/50, and remained at about this level for several hours, following which, over the next 12 hours, it rose to pretreatment levels. No significant alterations occurred in the serum cholinesterase activity at any time before, during, or after the abrupt drop in blood pressure.

I. *Benzodioxane.* One patient (M.C.) was given benzodioxane intravenously. During this procedure, her blood pressure rose slightly in the first one and one-half minutes, then gradually returned to the preinjection level. No significant alteration occurred in her serum cholinesterase activity.

J. *Rice Diet.* One patient (E.K.) was put on a strict rice diet for 17 days, which caused a moderate drop in blood pressure. No significant changes of serum cholinesterase were observed.

Discussion

The present studies indicate that no direct relationship exists between the cholinesterase activity of the serum and the arterial blood pressure. When the values for serum cholinesterase activity in 63 hypertensive patients were compared with those obtained from healthy subjects, no significant differences were noted. Furthermore, there was no correlation between the levels of serum cholinesterase activity and the levels of blood pressure of the hypertensive patients. In other experiments reported here changes in serum cholinesterase activity and in blood pressure were compared after administration of a variety of substances which are known or reported to affect serum cholinesterase activity or blood pressure. In most instances, significant drops in blood pressure were noted following injection of sodium amytal, and tetraethylammonium chloride. In one case a severe drop in blood pressure followed administration of veratrum viride. The rice diet produced a moderate fall in blood pressure. Cold pressor tests caused significant rises in blood pressure. With the other test substances (sterile saline, vitamin K, folic acid, and diisopropyl fluorophosphate) slight, but statistically insignificant, drops in blood pressure were noted. Benzodioxane produced a slight and statistically insignificant rise in blood pressure in the one subject on which it was tried.

The serum cholinesterase activity, on the other hand, was noted to drop significantly after administration of vitamin K, folic acid, tetraethylammonium chloride, sodium amytal, and diisopropyl fluorophosphate.

When changes in blood pressure were compared with changes in serum cholinesterase activity, no correlation could be noted between the fluctuations of these two factors in any of the experiments, and it was concluded that the fluctuations were independent of each other.

Summary

Normal levels of serum cholinesterase activity were found in a group of 63 unselected hypertensive patients. Seven patients were studied with a variety of drugs known to influence either blood pressure or serum cholinesterase activity, and the fluctuations in both factors were observed.

No correlation was noted between levels of serum cholinesterase activity and levels of blood pressure, nor could any correlation be established between the fluctuations of these two factors.

Significant drops in serum cholinesterase activity were noted following administration of vitamin K, folic acid, tetraethylammonium chloride and sodium amytal, and diisopropyl fluorophosphate.

It is concluded that no direct relationship exists between the blood pressure and the cholinesterase activity of the serum.

Acknowledgment

The author is indebted to Dr. Robert M. Kark for his help and guidance in the preparation of this manuscript, and to Dr. Robert W. Keeton for the privilege of studying patients on the wards of the Research and Educational Hospitals of the University of Illinois.

REFERENCES

[1] Antipol, W., Tuchman, L., and Schifrin, A.: Cholinesterase activity of human sera, with special reference to hyperthyroidism. Proc. Soc. Exper. Biol. & Med. **36:** 46, 1937.

[2] Davis, J. E., and Hamilton, W. M.: The influence of folic acid on serum cholinesterase activity in human subjects. Federation Proc. **6:** 95, 1947.

[3] Farber, M.: Serum cholinesterase in disease. Acta med. Scandinav. **114:** 59, 1943.

[4] Grob, D., Lilienthal, J. L., Harvey, A. M., and Jones, B. F.: The administration of diisopropyl fluorophosphate (DFP) to man. I. The effect on plasma and erythrocyte cholinesterase; general systemic effects; use in study of hepatic function and erythropoiesis; and some properties of plasma cholinesterase. Bull. Johns Hopkins Hosp. **81:** 217, 1947.

[5] Hall, G. E., and Lucas, C. C.: Cholinesterase activity of normal and pathological human sera. J. Pharmacol. & Exper. Therap. **59:** 34, 1937.

[6] Kunkel, H. G., and Ward, S. M.: Plasma esterase activity in patients with liver disease and with the nephrotic syndrome. J. Exper. Med. **86:** 325, 1947.

[7] Mazur, A., and Bodansky, O.: Mechanism of *in vivo* and *in vitro* inhibition of cholinesterase by DFP. J. Biol. Chem. **163:** 261, 1946.

[8] MICHEL, H. O.: Electrometric method for the determination of red blood cell and plasma cholinesterase activity. Federation Proc. **8:** 229, 1949.

[9] —: An electrometric method for the determination of red blood cell and plasma cholinesterase activity. J. Lab. & Clin. Med. **34:** 1564, 1949.

[10] MORELLI, A.: Cholinesterasi del siero ed ipertensione arteriosa. Progr. Med. Napoli **3:** 628, 1947.

[11] —, AND SALVI, P.: Terapia della ipertensione essenziale con vitamin K. Progr. med. Napoli **3:** 611, 1947.

[12] REICHERT, W., AND FRISCH, W.: Versuche über die Beziehung der cholinesterase zum Acetylcholin und zur Blutdruckhöhe. Arch. f. exper. Path. u. Pharmakol., **200:** 235, 1943.

[13] ROEPKE, M. H.: A study of cholin esterase. J. Pharmacol. & Exper. Therap. **59:** 264, 1937.

[14] SCHÜRTZ, F.: An effect of barbiturates on serum cholinesterase. J. Physiol. **102:** 259, 1943.

[15] TORDA, C., AND WOLFF, H. G.: Effect of vitamin K (menadione) on choline esterase activity, acetylcholine synthesis, and striated muscle. Proc. Soc. Exper. Biol. & Med. **57:** 236, 1944.

[16] VORHAUS, L. J., SCUDAMORE, H. H., AND KARK, R. M.: Measurement of serum cholinesterase activity in the study of diseases of the liver and biliary system. Gastroenterology **15:** 304, 1950.

[17] —, AND KARK, R. M.: Serum cholinesterase activity in the nephrotic syndrome. To be published.

[18] —, SCUDAMORE, H. H., AND KARK, R. M.: Effect of diisopropyl fluorophosphate on serum cholinesterase activity and on nitrogen balance. To be published.

[19] WESCOE, W. C., HUNT, C. C., RIKER, W. S., AND LITT, I. C.: Regeneration rates of serum cholinesterase in normal individuals and patients with liver damage. Am. J. Physiol. **194:** 549, 1947.

Dihydrogenated Ergot Alkaloids in the Treatment of Essential Hypertension

By HOMER J. DUPUY, M.D., JOHN SIGNORELLI, M.D., AND ALBERT M. ATTYAH, M.D.

The effect of the oral and intravenous administration of the dihydrogenated ergot alkaloids on 25 cases of essential hypertension in the age group of 25 to 56 is reported with reference to (1) incidence of hypotensive effect, (2) degree of hypotensive effect, (3) duration of the hypotensive effect.

A NEW preparation, C.C.K.-179, a combination of equal amounts of dihydroergocristine, dihydroergokryptine, and dihydroergocornine, has recently been used in the treatment of hypertension. The theoretic and experimental basis for the trial of this preparation has been adequately elucidated by Nickerson.[1] Conflicting results from clinical trials have been reported.[2] Experimentally, certain hypotensive effects of the dihydrogenated ergot alkaloids have been demonstrated. The following theories have been postulated as to the mode of action of this group of drugs: (1) direct depression of the central vasomotor center with supposed concomitant stimulation of a vasodepressor center; (2) adrenergic blockade (so called adrenolytic and sympathicolytic activity); (3) vagotonic action.

In "neurogenic hypertension" the adrenergic blockade activity would be most important. Unfortunately, we find this type of hypertension to be most unusual clinically. In essential hypertension all three mechanisms may be of varying relative importance. Of course, the dihydrogenated ergot alkaloids have other physiologic actions, some of which may tend to counterbalance the hypotensive mechanism. Prominent among the other actions is probably the smooth muscle constricting action,[3] and possibly the depression of renal blood flow which has been reported.

We feel that therapy in the management of arterial hypertension, to be adequate, must not only lower blood pressure but must arrest or reverse the progressive pathologic lesions of the vascular tree. These lesions are far more significant than the height of the blood pressure and do not necessarily parallel blood pressure elevation. The best presently available objective means of detecting a therapeutic response in essential hypertension is probably a serial determination of the blood pressure and eye ground studies with an adequate pre- and post-therapy control period; at least, until the basic etiologic factors of essential hypertension are definitely known.

The 25 patients to whom we gave a trial on oral C.C.K.-179 have been followed by us, on an ambulatory basis, at frequent intervals for a period of 18 to 36 months. Most were seen in a special hypertension clinic. We are acquainted with the social and economic status of these patients, and with the individual variations of the blood pressure of each. Many have a good lay knowledge of the disease and can at times cite factors affecting the heights of their blood pressure. Compared with the usual untrained patient, these patients are less suggestible in reporting symptoms. In all patients the diagnosis of essential hypertension was adequately confirmed by physical findings and laboratory studies.

This group consisted of 17 Negro and 8 white patients; 8 males, 17 females. The average age was 40.4 years with extremes of 25 and 56. The average blood pressure of the group was 190/100. The extremes of blood pressure were 155/90 to 248/150.

The drug was administered in two forms: 1 mg. tablets and a liquid form containing 1 mg. of C.C.K.-179 in 1 cc. of vehicle. The individual patients were started on small doses

From the Hypertension Clinic, L.S.U. Unit, Charity Hospital; and Department of Medicine, Louisiana State University School of Medicine, New Orleans, La.

Drugs used for this experiment supplied by the Sandoz Company.

which were gradually increased. The average maximum daily dose was 7.5 mg. in tablet form and 5.6 mg. in liquid form. The daily maximum dose was maintained for a minimum of one week. The extremes of daily dosage (tablets) were 3 mg. and 10 mg.; and (liquid) 2 mg. and 10.6 mg. Therapy was continued for from three weeks to three months. Alarming side effects were not encountered, probably because the dosage was not pushed to serious individual toxicity. Nevertheless, four patients had mild nausea, two had dizziness, and three experienced drowsiness. Because of these effects, several patients requested that the drug be discontinued.

One patient showed a significant blood pressure drop from 228/140 to 198/110 with a concomitant alleviation of headache. On discontinuing the drug the blood pressure slowly rose to pretreatment levels. This drop occurred on a dosage level of 8 to 9 mg. daily. A second patient had an equivocal drop in blood pressure (15 to 30 mm. Hg systolic, 0 to 15 mm. Hg diastolic). We could not maintain this drop in pressure because of drowsiness and "lack of energy" at the dose necessary for this effect, 10.6 mg. daily of the liquid form of C.C.K.-179. Twenty-three of 25 patients had no changes in blood pressure other than variations no greater than those noted prior to administration of the drug.

In addition to the above cases, two patients with hypertension were given 0.2 mg. of C.C.K.-179 intravenously over a five minute period. Both patients showed a fall in blood pressure within the first eight minutes, with a systolic drop of 50 mm. Hg and an average diastolic fall of 20 mm. Hg. However, both patients exhibited a return of blood pressure to pre-injection levels by the end of 45 minutes. Essentially the same results were obtained in two cases of chronic glomerulonephritis and one case of acute glomerulonephritis with hypertension. Subjective manifestation in all of these cases consisted of warmth, tingling of skin of the face and extremities, and headache which began within the first two minutes of injection and lasted approximately 10 minutes.

Conclusion

We do not doubt that the dihydrogenated ergot alkaloid preparations are capable of lowering blood pressure when given in sufficiently large doses, intravenously and orally. However, from a clinical standpoint we do not feel that the particular compounds we used have any practical application in the management of an individual with essential hypertension because of

(1) the extreme low incidence of hypotensive effect;

(2) the minimal degree of hypotensive effect when this result was obtained; and

(3) the short duration of the hypotensive effect of the intravenous form of the compound.

Acknowledgment

We wish to express our appreciation to Miss Rosemary Carrere, Junior League voluntary social worker, for her assistance in this project.

REFERENCES

[1] Nickerson, M.: The pharmacology of adrenergic blockade. J. Pharmacol. & Exper. Therap. **95:** 27, 1949.

[2] Gast, W., and Huber, E. F.: Treatment of hypertension with mixture of hydrogenated alkaloids of ergot. Wien. klin. Wchnschr. **62:** 893, 1950.

[3] Crosley, A. P., Jr., Cummins, A. J., Barker, H. G., and Clark, J. K.: Renal hemodynamic effects of dihydroergocornine (DHO-180) in man. J. Pharmacol & Exper. Therap. **98:** 138, 1950.

Abdominal Aortic Aneurysm with Rupture into the Inferior Vena Cava

By WILLIAM N. VIAR, M.D., AND THOMAS A. LOMBARDO, M.D.

A patient is presented with an arteriosclerotic abdominal aneurysm that ruptured into the inferior vena cava. Clinically, the picture was that of a peripheral arteriovenous communication with heart failure of the "high-output" type. Intestinal bleeding occurred as a result of venous engorgement and hemorrhagic colitis.

ANEURYSM of the abdominal aorta is a rare finding. Osler[1] reported 11 instances of abdominal aneurysm out of 2200 necropsies performed at the Johns Hopkins Hospital. Later, at the same institution, he found 16 cases of abdominal aortic aneurysm among 18,000 necropsies The first case, according to Osler, was reported by Vesalius in 1567.

Rupture is the characteristic course of the disease. Most often the rupture occurs into the retroperitoneal tissues, the next in frequency being into the peritoneal cavity; a considerable number of instances of rupture into the gastrointestinal tract have been reported as well. Of course rupture may occur into any structure in the abdominal cavity but, as far as we have been able to determine, there has never been a reported case of abdominal aortic aneurysm with spontaneous rupture into the inferior vena cava. It is because of the rarity of this condition that this report is being made.

CASE REPORT

W. B. H., a 69 year old white retired attorney was seen on January 10, 1951, with the chief complaint of generalized aching and lower abdominal cramps. The pain was said to start in the left lower quadrant and to radiate across the lower abdomen to the right lower quadrant. This pain would persist for only a few seconds, and would return every 5 to 10 minutes. Anorexia and some nausea, but no vomiting or diarrhea, were found. The past history was irrelevant except that diverticulosis of the colon had been found when x-ray studies had been made almost 10 years previously.

Physical examination at this time revealed the blood pressure to be 150/90, with no other abnormal findings. After three days in bed he developed lower abdominal tenderness to deep palpation with some abdominal distention, and was expelling large amounts of gas both by mouth and by rectum. At this time it was thought that the patient had diverticulitis with partial intestinal obstruction. He was hospitalized and x-ray studies were made. These revealed numerous distended loops of small bowel. There was a moderate amount of gas within the colon, with a distended loop in the left upper quadrant. There was a rounded area of calcified density in the right upper quadrant which suggested a gallstone. No fluid level was seen. No other masses or soft tissue shadows were visible. X-ray findings were thought to be compatible with intestinal obstruction. He was treated with penicillin, streptomycin, and sulfathalidine. He improved on this regime but continued to have some lower abdominal cramping. On the third hospital day he was discovered to have an abdominal mass about the size of an orange. This was situated a little more to the right of the midline than to the left. During the next few hours the mass increased in size and a continuous murmur over it was noted. The next morning an associated continuous thrill was found over the mass. It was thought at this time that the mass represented aneurysmal dilatation with an arteriovenous communication, most likely between the aorta and the inferior vena cava. The blood pressure was 140/40 and there was a typical Corrigan pulse.

Four days later bleeding from the rectum occurred but this promptly subsided following the administration of morphine. During the remaining six weeks of his life there was constant severe anorexia, and, after taking food, nausea would become evident. In addition, he developed progressive right-sided heart failure which responded poorly to digitalis and mercury. All the typical signs of a high cardiac output were present during this time. The loud continuous murmur and the pronounced thrill continued to be present over the abdominal mass. He became progressively more edematous in spite of therapy, and it finally became necessary to make puncture holes in his legs to allow the fluid to drain. This procedure was associated with a 30 pound weight loss. However, he continued to lose strength as the result of starvation.

From the Department of Medicine, The Medical College of Alabama, Birmingham, Ala.

Seven weeks after the onset of illness, bleeding from the rectum recurred and the patient expired.

Final Clinical Diagnosis. Diverticulitis, with inflammation extending to the wall of an already arteriosclerotic aorta, with consequent dilatation and dissection, and early rupture into the inferior vena cava. It was thought that death was probably brought about by rupture of the aneurysm into the gastrointestinal tract.

FIG. 1. The white rough-looking vessel at the top of the photograph is the open aorta just above the aneurysmal mass. The opened vessel on the left side of the aneurysmal mass with the smooth shiny surface is the inferior vena cava. The round opening in the lower end of the last named vessel is the communication between the inferior vena cava and the aneurysmal sac of the aorta.

Autopsy Findings. (The postmortem examination was performed by Drs. Roger Baker and Raymond Stokes, of the Pathology Department, Medical College of Alabama.)

The aneurysm measured 13 cm. across. There was an opening 1 cm. in diameter with rolled edges between the aneurysm and the inferior vena cava (fig. 1). "Apparently this arteriovenous fistula caused great pressure in the venous side of the circulation and one notes that the right side of the heart is greatly dilated." The left side of the heart was also dilated, "but there was no edema and not much congestion in the pulmonary circuit, which one would expect if the pressure were exerted back through the lungs from the left side of the heart." Microscopic section of the aneurysm indicated that it was atherosclerotic in nature.

Sections of the right coronary artery revealed severe atherosclerosis and old fibrous thickening with recanalization. There was one point of hemorrhage into the wall of this artery. Much fibrosis was noted in the heart muscle but no evidence of a recent infarction.

There were peptic ulcers in the duodenum and stomach which revealed characteristic findings denoting that they had been present for a long while. Agonal perforation of the duodenal ulcer had occurred. There was tremendous venous distention of that portion of the lower bowel drained by the inferior vena cava, and hemorrhagic colitis. "We interpret the bleeding from the lower bowel as probably a matter of bleeding from the hemorrhagic mucosa of the large bowel." Chronic diverticulitis was also present.

DISCUSSION

Abdominal aortic aneurysm is found in approximately 0.09 per cent to 0.3 per cent of all cases coming to autopsy.[2, 3] It is less common than aneurysm of the thoracic aorta.[1, 4] This difference is decreasing.[5, 6] This declining ratio is best explained by the fact that: (1) thoracic aneurysms are usually syphilitic, and syphilis is becoming less frequent as a consequence of more effective treatment, and (2) abdominal aneurysms are usually arteriosclerotic, and arteriosclerosis is increasing because people are living longer.

Abdominal aortic aneurysms are caused primarily by syphilis and arteriosclerosis. Those due to syphilis occur in people of 50 years of age or less, the majority appearing in the fourth and fifth decades; and those of arteriosclerotic origin in people 50 years of age or over, the majority appearing in the sixth and seventh decades.[7]

Men are much more likely to have abdominal aortic aneurysms, the majority of the syphilitic variety occurring in male Negroes.[5, 7–8]

Syphilitic aneurysms usually originate at or above the renal arteries, and are of the saccular variety, while those of arteriosclerotic origin ordinarily arise below the renal arteries and are usually of the fusiform variety.

Syphilitic aneurysms produce symptoms early. Because of vertebral erosion, pain is usually the first symptom. It is usually constant and boring in character. It may throb and become much more severe at night. If pressure is produced on nerve roots, characteristic radicular pain occurs. Pressure on contiguous structures, especially the gastrointestinal tract, may produce anorexia, nausea and vomiting, or renal colic if the ureter is obstructed or a kidney displaced.

Arteriosclerotic aneurysms, due to their more anterior location, either remain asymptomatic entirely (80 per cent of one series[7]) or produce symptoms only at a late stage. The classic and usually the first symptoms from arteriosclerotic abdominal aneurysms are those produced by rupture of the aneurysm.

The most likely place of rupture is into the retroperitoneal tissues. Next in frequency is rupture into the peritoneal cavity, and, rarely, into the gastrointestinal tract. Karabin[9] presented an excellent report analyzing symptoms produced by retroperitoneal hemorrhage.

If rupture occurs into the gastrointestinal tract, rapid exsanguination occurs. Melena without rupture into the gastrointestinal tract may occur as a result of venous congestion secondary to obstruction or rupture into the inferior vena cava. Melena may also result from pressure on the gastrointestinal tract alone, as in the case reported by Coggeshall and Genovese.[10]

Diagnosis was made simple in our case because the mass developed so quickly and produced such outstanding signs. The abdominal pulsations were so great that the bed would move with each pulsation. The mass was expansible, easily felt, and the murmur was very loud. The rupture occurred early into the inferior vena cava, and classic signs of an arteriovenous communication became apparent. The murmur became continuous and machinery-like in type, and a continuous thrill was easily detected. The diastolic blood pressure dropped from 90 mm. Hg to 40 mm. Hg, and the classic pulse pressure of the "overactive" heart was produced.

Consequent to rupture of the aorta into the inferior vena cava, there was a marked increment in venous return to the heart (increased inflow load). This burden on a heart already impaired by myocardial fibrosis led to the typical picture of "high-output failure."

The intestinal bleeding in this patient was due to ulceration of the engorged venous channels of the lower bowel, which developed consequent to establishment of the arteriovenous shunt with a great rise in venous pressure.

Summary

A patient is reported with rupture of an arteriosclerotic aneurysm of the abdominal aorta into the inferior vena cava. The diagnosis can be made readily when a patient presents: (1) a pulsating abdominal mass; (2) a continuous murmur with systolic intensification over the mass; (3) a collapsing pulse; and (4) the typical signs of an overactive heart with increased output.

In the patient reported, rectal bleeding was due to excessive venous engorgement without rupture of the aneurysm into the alimentary tract.

REFERENCES

[1] Osler, W.: Aneurysm of the abdominal aorta. Lancet **2:** 1089, 1905.

[2] Rattino, A.: Aneurysms of the abdominal aorta, with rupture into the duodenum. Am. Heart J. **25:** 826, 1943.

[3] Epstein, J.: Aneurysms of the abdominal aorta. Ann. Int. Med. **22:** 252, 1945.

[4] Luche, B., and Rea, M. H.: Studies on aneurysms. J. A. M. A. **67:** 935, 1921.

[5] Saleeby, E. R., and McCarthy, P. A.: Aneurysms: a statistical study of 84 cases from the Surgical Department of the Philadelphia General Hospital. Pennsylvania M. J. **11:** 969, 1938.

[6] Ruffin, M. deG., Castleman, B., and White, P. D.: Arteriosclerotic aneurysms and senile ectasia of the thoracic aorta. Am. Heart J. **22:** 458, 1941.

[7] Scott, V.: Abdominal aneurysms: a report of 96 cases. Am. J. Syph., Gonor. & Ven. Dis. **28:** 682, 1944.

[8] Bryant, J. H.: On aneurysms of the abdominal aorta. Clin. J. (London) **23:** 71, 1903.

[9] Karabin, J. E.: Retroperitoneal hemorrhage with special reference to the accompanying paralytic ileus. Am. J. Surg. **56:** 471, 1942.

[10] Coggeshall, W. E., and Genovese, P. D.: Rupture of an abdominal aneurysm associated with massive gastrointestinal hemorrhage. Am. Heart J. **40:** 789, 1950.

CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Surgery for Mitral Stenosis

A Review of Progress

By EDWARD F. BLAND, M.D.

THE PAST five years have witnessed a widespread renewal of interest in operations for mitral stenosis. Our surgical colleagues have pushed forward with courage, skill, and notable success, their efforts to relieve the obstructed mitral orifice. It is the purpose of this report to review briefly the background of this revival, to summarize the more recent developments and, with the cooperation of those most concerned, to appraise the results and the risks involved. Our interest is primarily from the point of view of the patient and his physician; surgical technics are not our concern.

EARLY CONTRIBUTIONS

A capitulation of the attempts in the past to break down the barrier of stenotic valves is a fascinating exposition of boldness, persistence, and futility. Until the turn of the century the prevailing views as to the surgical sanctity of the heart were epitomized by the renowned Billroth in 1883: "Let no man who hopes to retain the respect of his medical brethren dare to operate on the human heart."

However, the advent of asepsis, experimental laboratories, and another century opened new vistas. It was Sir Thomas Lauder Brunton (of amyl nitrite fame) who proposed in 1902 the possibility of surgical intervention for mitral stenosis. Although this precipitated a vigorous and somewhat sarcastic editorial in the next issue of the London Lancet of that year,[31] it served to stimulate further the experimental approach which had already demonstrated in animals the feasibility of such a procedure (Klebs, 1876), and led to the subsequent studies of MacCallum (1906), Cushing and Branch (1908), Bernheim (1909), and Schepelmann (1912).

Thus was the stage set for the first attempt in a human being by Doyen in 1913. Instead of a patient with mitral stenosis, he chose a young woman of 20 with congenital pulmonary stenosis, and he attempted to relieve the obstruction with a tenotome knife passed through the right ventricle. The patient expired a few hours later and necropsy revealed a tubular narrowing of the conus (as is often the case) rather than a localized stenosis of the valve.

A year later Tuffier (1914) exposed the heart of a young man with advanced aortic stenosis. It was his intention to insert a knife above the aortic ring and incise the stenosed valve, but during the operation this plan was abandoned. Instead, dilatation of the stenosed orifice was accomplished by invaginating the wall of the aorta with the forefinger. The patient survived and was reported living and possibly improved 10 years later.

Thereafter another decade elapsed and the extensive experience with cardiac wounds in World War I accrued before further attempts were forthcoming.

In 1923 Cutler and Levine reported the first case of a successful section of the valve for advanced mitral stenosis.[24] The patient, a girl of 11 years, had been observed for eight months at the House of the Good Samaritan (Boston) with recurring episodes of acute dyspnea and hemoptysis, and because of the increasing gravity of her symptoms she was transferred to the Peter Bent Brigham Hospital for surgery. A tenotome knife was passed through the left

From the Massachusetts General Hospital, Boston, Mass.

ventricle and an attempt made to incise each cusp of the obstructing mitral ring. Although the postoperative state was critical, the patient survived, but the signs of mitral stenosis persisted; the diastolic murmur was slightly altered and there was a prolongation of her systolic murmur. She lived four and a half years after operation, but her activities were seriously limited and she required hospitalization on several occasions for rest and treatment. She finally succumbed with bronchopneumonia and extensive congestion of the lungs.

Necropsy revealed moderate stenosis of the valve, but the orifice admitted a bougie 4 cm. in circumference. The site of the previous incision was easily recognized by a defect in the thickened rolled edge of the valve ring joined towards the base by a thinner membrane-like structure (fig. 1). There seemed no doubt the orifice had been enlarged by the operation. Furthermore, there was no suggestion of an overgrowth of scar tissue in the healing process. This is a key case: it not only represents the first survivor of valve section but the subsequent four and a half years of life also provide an indication of the favorable type of valve healing hoped for in those now being submitted to surgery.

During the next five years (1923–28) Cutler and his associates undertook a somewhat similar procedure in six additional patients: none survived.[23] Allen, also in 1923, attempted to approach the valve through the left atrium with a cardioscope devised by Allen and Graham,[6] but the patient succumbed during the procedure.[5]* Souttar (1925) successfully dilated the mitral ring by finger and his patient survived (a forerunner of the present most favored procedure), but Pribram's attempt (1925) with a valvulotome through the left ventricle ended fatally on the fifth day.

Thus, during the 1920's 10 patients with mitral stenosis were subjected to valve section or digital dilatation as follows:

Cutler and associates (section)	7 (1 survived)
Allen (cardioscope)	1
Souttar (dilatation)	1 (survived)
Pribram (section)	1

FIG. 1. Photograph of the mitral valve of Cutler and Levine's patient who lived four and one-half years after valvulotomy. The site of incision was easily recognized by a defect in the thickened rolled edge of the valve ring joined at the base by the thinner membrane-like structure. (Cutler and Beck: Arch. Surg. **18:** 403, 1929.)

The 80 per cent mortality was discouraging. However, in spite of this unfavorable experience, interest at the laboratory level continued, and between 1929 and 1932 Powers was successful in producing in dogs gross deformity of the mitral cusps by electrical coagulation followed by infection with intravenous inoculations of *Streptococcus viridans*.[50] Later healing in those who survived yielded a scarred valve with an element of stenosis. Subsequent valvulotomy led to acute cardiac dilatation and failure in the majority of the animals.[51] From these experiments he concluded that the abrupt creation of mitral regurgitation was a hazardous procedure which in man might likewise lead to acute decompensation and death.

* It is of interest, particularly for historical accuracy, to note that since the earlier reports of Cutler and Beck,[23] and including the more recent ones of Harken,[40] of Bailey,[8] and of others,[10] reference to this case operated upon in 1923 has been erroneously cited as "Allen, D. S., and Graham, E. A.: J. A. M. A. September 23, 1922," and "Allen, D. S.: Arch. Surg. January, 1924."

A careful check of these two references reveals no mention whatsoever of a human case. In view of this discrepancy and the obvious error perpetuated through almost a quarter of a century, and in response to a personal communication from the author, Dr. Evarts A. Graham kindly supplied the correct reference to the original report by Dr. Duff S. Allen.[5]

Clinical support for this deduction was inferred from the remarkable case recorded by Adam (1927) of perforation of the anterior leaflet of the mitral valve by a bullet in a young man of 19 who attempted suicide but survived. He was left with the sign of pure mitral regurgitation—a loud blowing systolic murmur at the cardiac apex. He lived 10 years, but his course was marked by progressive cardiac enlargement, auricular fibrillation, chronic congestive failure, and death. A photograph of this unique specimen is reproduced in figure 2, since, as in Cutler and Levine's case, it gives a clue to the type of healing which occurs following valve trauma (and surgery). Healing around the defect had been accompanied by only minimal thickening of the adjacent valve substance. It is of further interest that as a result of regurgitation all the heart chambers in this case were greatly hypertrophied and dilated.

FIG. 2. Photograph of perforation of the anterior leaflet of the mitral valve (bullet wound) in Adam's patient who survived 10 years with pure mitral regurgitation. (Adam: Ztschr. Kreislaufforsch. **19:** 313, 1927.)

Thus it is understandable that these combined clinical and laboratory failures temporarily discouraged further attempts at valve surgery until after World War II. In the interim, from a combination of circumstances, there evolved slowly an attitude of renewed confidence where heretofore the dismay of former failures had prevailed. Notable in this connection were the remarkable results obtained in the correction of congenital defects, as well as the favorable experience with cardiac wounds in another world war—this time with the actual removal of missiles from the heart cavities—and finally, there emerged a new generation of dynamic surgeons, fully fortified with catheterization data[21, 36] and hydraulic formulas.[35] The inevitable outcome was a more sustained and successful attack upon the obstructing valve.

COLLATERAL PROCEDURES

Discouraged by the prohibitive mortality of the earlier efforts to relieve mitral stenosis by a direct approach, others sought an indirect solution to the problem.

A special challenge was presented by those patients with high grade stenosis, little or no cardiac enlargement, and recurring (sometimes fatal) attacks of acute pulmonary congestion and hemorrhage. Their disability clearly involves extreme pulmonary hypertension behind an obstructed valve outlet, secondary alterations in the lungs, and a strong right ventricle. Under conditions of stress, tachycardia, and increased blood volume the augmented activity of the hypertrophied right ventricle floods the lungs whose outlet is fixed by the narrowed mitral orifice. Under these circumstances pulmonary edema and hemorrhage are inevitable. It is an acute increment in the already excessive pulmonary pressure which is responsible for this vascular crisis within the lungs (fig. 3). Medical measures (digitalis, diuretics, and diets), although helpful, are ultimately ineffective in dealing with this clinical paradox.

Two clues exist which suggest that help might be available for them outside the heart. In 1926 Jarotzky called attention to the apparent protection afforded the lungs in patients with mitral stenosis who had a congenital atrial septal defect (Lutembacher's syndrome). The protective action of this defect in lessening pulmonary hypertension and congestion has been substantiated by clinical observation,[11, 16] and by catheter studies.[27] Jarotzky suggested that the surgical creation of such a defect might be helpful, as did O'Farrell in 1938. This was actually accomplished by Harken in 1948 but has now been abandoned in favor of the direct operation upon the valve.[40]

Another clue in a different direction is presented by the remarkably dilated bronchial

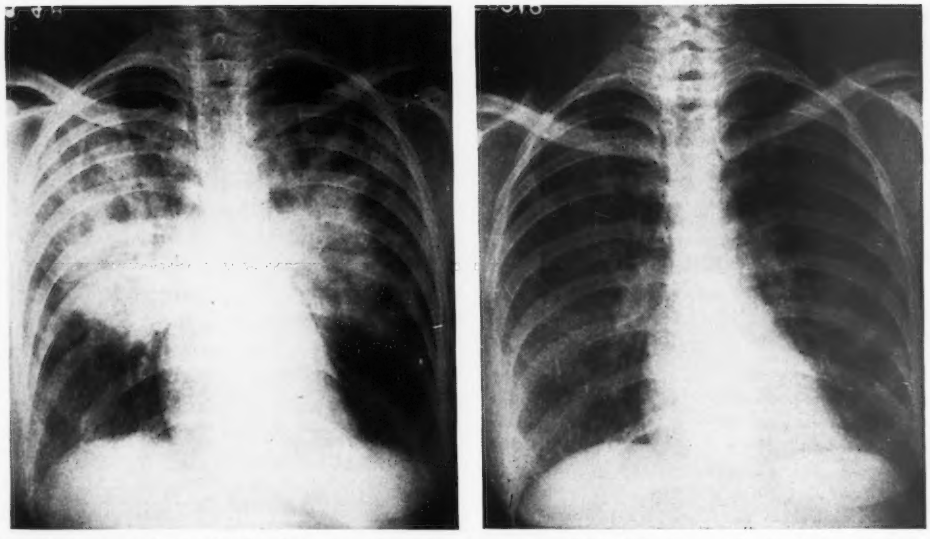

FIG. 3. Acute and near fatal pulmonary edema in a woman aged 24 with advanced mitral stenosis but with little or no cardiac enlargement. *Left.* Roentgenogram on entry showing extensive edema of the lungs with characteristic butterfly distribution. *Right.* Roentgenogram three days after rapid subsidence of the edema.

veins in patients with longstanding mitral stenosis—an attempt by nature to provide an outlet from the congested pulmonary bed into the systemic veins.[32] Thus, in those whose pulmonary syndrome is characterized by massive hemorrhage from these dilated varices (on occasion up to 500 cc.), the accompanying edema is often strikingly relieved or actually aborted. It is unfortunate that this natural protective mechanism sometimes leads to fatal exsanguination.[49]

In 1946, with these facts in mind, Bland and Sweet decided that a vent from the high pressure area of the left atrium or adjacent pulmonary veins into a systemic vein might offer relief to these patients. At that time an extracardiac shunt seemed less risky than either an intracradiac septal defect or a direct operation upon the valve. After two more years of deliberation and study the operation was successfully performed (March 1948) on a 17 year old girl.[16, 17, 59] An anastomosis was effected between a branch of the right inferior pulmonary vein and the azygos vein (fig. 4). A vigorous diversion of blood from the pulmonary circuit into the systemic vein ensued. Direct measurements of left intra-atrial pressure in later cases confirmed the hope that a significant lessening of tension would result. The subsequent course of this patient was so remarkable, and the animal experiments of Swan were so encouraging, that during the following two years (1948–49) 12 patients with recurring severe pulmonary edema were likewise operated upon, and more recently two additional patients have had this procedure. Certain physiologic data

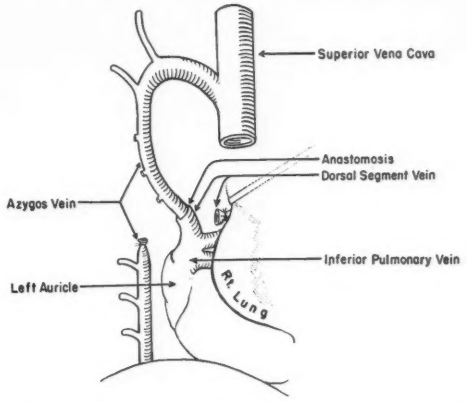

FIG. 4. Diagram of the pulmonary-azygos shunt viewed from the right side. The lung has been retracted forward. Oxygenated blood from the high pressure pulmonary circuit escapes backward through the anastomosis to the low pressure systemic bed distending the azygos vein to its juncture with the superior vena cava. (Bland and Sweet: J. A. M. A. **140:** 1259, 1949.)

assembled at the time of operation are shown in table 1. It is to be noted that the pressure by direct measurement in the left atrium was from four to five times normal in all instances, and upon release of the shunt there usually occurred within a few moments a prompt drop of approximately 80 mm. of saline (unpublished data, Bland and Sweet, 1951).

The later course of this group has been of special interest. Fully half have had striking and continued relief from pulmonary edema, several were much benefited for one to two years but are now beginning to have milder recurrences of their previous trouble (suggesting a possible closure of the shunt), a few had only questionable benefit, and three succumbed within a few days of the procedure.

TABLE 1.—*Measurements made at operation by means of a needle passed into the left atrium (usually through a pulmonary vein) and recorded in millimeters of saline before and after release of the shunt. (Bland and Sweet, unpublished data, 1951.)*

ADVANCED MITRAL STENOSIS

LEFT AURICULAR PRESSURE

Direct Measurements at Operation
(Normal = 100 ± mm. H_2O)

CASE	SHUNT CLOSED	SHUNT OPEN
I. O.C.	460	
3. R.O.	425	390
4. D.G.		450
5. A.P.	530	370
6. E.R.	460	370
7. L.G.	480	370
8. E.J.	300	180
9. E.P.	475 ?	475
10. A.O.	370	350
12. R.J.	440	
13. T.R.	510	430
AVERAGE OF 8 COMPLETED CASES	447 (80)	367

As was emphasized originally by the authors, this procedure is at best a compromise and not a cure. It was designed only for those with relatively small strong hearts as a protection to the lungs.

In France, d'Allaines and associates, unaware of this earlier work in Boston, performed a somewhat similar procedure (January 1949) and subsequently operated on 16 additional patients with encouraging results in the majority,[2, 3] but they have now shifted to the direct approach (as have Bland and Sweet) as a more promising and less difficult operation.[43]

These purely palliative measures of the past three years have now been overshadowed and quite properly replaced in large measure by the direct attack upon the mitral valve. The remarkable improvement in technic and the consequent lessening of the risk have rendered other methods less attractive and somewhat obsolete, but nevertheless useful, perhaps, under special circumstances where complicating aortic valve disease (regurgitation) already places a strain upon the left ventricle.

Direct Operations

Concurrently with the foregoing developments, a more aggressive attack upon the valve itself by several groups has yielded remarkable results, a colorful glossary of terms (valvuloplasty, commissurotomy, finger-fracture, and stenotomy) and, in certain quarters, even a new philosophy which intimates that all patients with mitral stenosis should have their valves split.

In the forefront, and a brilliant exponent of this resurgent interest in valve surgery, was H. G. Smithy, Jr. His untimely death in 1948 at 34 was a tragic loss—he was himself a victim of aortic stenosis. Through the continuing efforts of Harken in Boston, of Bailey in Philadelphia, of Blalock in Baltimore, and of Brock in London, as well as of others elsewhere, enough data have now accumulated to warrant an appraisal of the present status and future promise of the direct approach. I am indebted to these surgeons and in particular to their medical associates* for permitting me to pool their results for the purpose of this report. Minor differences of opinion exist as to technics and indications, but there is wholehearted agreement as to the immediate benefits to be

* I am especially indebted for personal communications concerning the medical aspects of the operated cases from Drs. E. Cowles Andrus (Baltimore), Maurice Campbell (London), George C. Griffith (Los Angeles), and Prof. J. Lenègre (Paris).

expected, of respect for the risks involved and of the uncertainties of the future.

In regard to technic, all agree that the approach through the left atrial appendage is safest and surest. Most surgeons prefer digital dilatation, with "finger-fracture" when possible, as less risky than incision in a blind field with a valvulotome. It is clear, however, that each method has a place. In general, calcified valves fracture more readily than heavily scarred and gristly structures. Unfortunately, a few are encountered for which neither method is adaptable. In the author's clinic the following situations have rendered operation either impossible or prohibitively risky: (1) a markedly gristly, funnel-shaped valve, impossible to fracture or to incise successfully even at the autopsy table (postmortem case); (2) an abnormally narrow communication (less than 1 cm. diameter) between the appendage and atrial cavity, plus structural deformity rendering the alternative approach through a pulmonary vein too dangerous; (3) a high degree of mitral regurgitation evident at operation in spite of "unequivocal" clinical and catheter evidence of high-grade pure mitral stenosis.

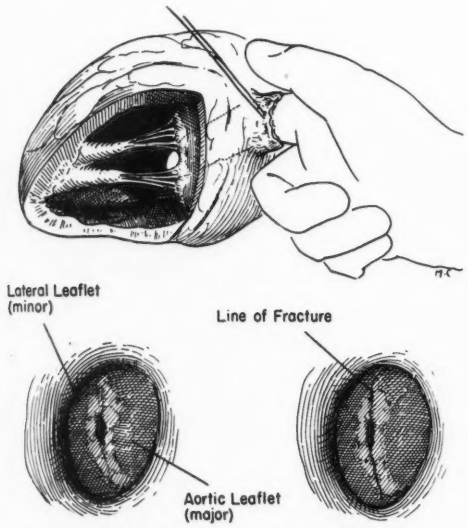

FIG. 5. Diagram of finger-fracture valvuloplasty. The index finger is passed through the left auricular appendage and left auricle to reach the mitral orifice. (Courtesy of Dr. Dwight E. Harken, 1951.)

Figure 5 illustrates the most favored procedure, so-called "finger-fracture valvuloplasty" (Harken). It has been emphasized by Harken and his associates, and substantiated by others, that incision in the region of the anterior cusp is followed by far greater regurgitation than is an operation on the posterior cusp (selective insufficiency) or resection of the immobilizing commissure bridges.[40] Bailey and his group prefer incision in the region of the obliterated commissures which favors (in agreement with Harken) less regurgitation and more effective valve function—so-called "commissurotomy" (Durant), as shown in figure 6.[8, 33, 34] More recently a less descriptive but more inclusive term, "stenotomy," has been suggested for both procedures (Alroy).

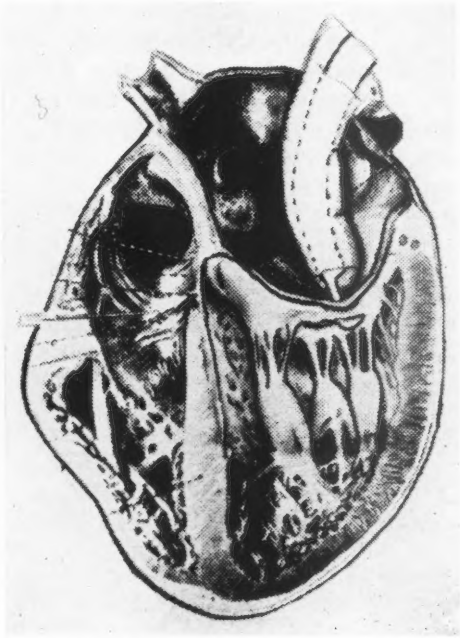

FIG. 6. Diagram of commissurotomy. The right index finger bearing the commissurotomy knife has been inserted through the left auricular appendage and the hooked blade engaged on the lateral commissure. (Glover, Bailey and O'Neill: J. A. M. A. **144:** 1049, 1950).

An ingenious and different approach has been undertaken by Murray. A cardioscope is passed through the left ventricle, and the mitral valve

is resected. In order to compensate for the resulting regurgitation, a sling-like structure composed of a section of vein, everted and supported with a length of tendon, is suspended on the ventricular side of the orifice for a ball-valve action. Of 10 patients, there were eight survivors. It would seem, however, that this procedure is too complicated and too unphysiologic to offer promise.

For the special purpose of this report a survey of the experiences in selected centers in this country and abroad indicates that during the past three years, 352 patients with mitral stenosis have been operated upon, and from collateral reports of operations elsewhere it is quite likely that the total now approaches 500 cases.

An early and dramatic improvement has occurred in the majority of patients. Further clinical observation and catheter studies support the substantial benefits predicted from the early improvement.[26, 29]

Selection of Cases

The selection of patients for either of these formidable procedures must of necessity rest largely with the internist and cardiologist. This aspect has been emphasized recently by Harken and co-workers.[39] I am indebted to the internists intimately associated with the surgeons listed in table 2 for their opinion and criteria in the selection of patients.

In general it is agreed that the most suitable cases are those with a high degree of mitral stenosis with little or no evident regurgitation, and with unmistakable signs and symptoms of pulmonary engorgement (dyspnea, cough, pulmonary edema, or hemoptysis). The smaller the heart, the better the outlook. Those with large hearts and chronic congestive failure are poor risks and are unlikely to benefit significantly from surgery. Auricular fibrillation or previous embolism increase the hazards slightly but do not constitute contraindications per se. It is unlikely except in special instances that worthwhile benefit can accrue for patients beyond 50 years of age.

There are two absolute contraindications to surgery: active rheumatic carditis and bacterial endocarditis. Measurable strain on the left ventricle from aortic regurgitation (less often stenosis) or from mitral regurgitation renders

Table 2.—*Operations for Mitral Stenosis**

	Cases	Mortality	Embolism	Improved
Bailey et al.[9] (Philadelphia)	165	17 (10.3%)	9 (5.4%)	"majority"
Harken et al.[34] (Boston)	62	17 (27.4%)	4 (6.4%)	"majority"
Brock et al.[19] (London)	50	8 (16.0%)	2 (4.0%)	37 (74.0%)
Blalock et al.[14] (Baltimore)	30	2 (6.6%)	1 (3.3%)	26 (86.9%)
Longmire et al.[44] (Los Angeles)	25	4 (16.0%)	4 (16.0%)	"most"
Brantigan[18] (Baltimore)	12	3 (25.0%)	1 (8.3%)	7 (58.3%)
Author's series (Boston)	8	2 (25.0%)	0	6 (75.0%)
Totals†	352	53 (15.0%)	21 (6.0%)	

* As of approximately May 1951. † Operations by Drs. J. G. Scannell and R. H. Warren.

In table 2 are summarized the results furnished the author (mostly as of May 1951) from seven centers. The 352 cases include the early and hence most unfavorable types; thus the mortality figures are weighted in an unfavorable direction. With rapid improvement in technics and a more discriminating selection of patients, there has been a gratifying improvement in the results, so that now a fair estimate indicates a 10 to 15 per cent operative risk for those patients with relatively slight to moderate cardiac enlargement but with advanced mitral stenosis and severe pulmonary hypertension, and a correspondingly greater risk for those with larger and weaker hearts. The further hazard of postoperative embolism, although often nonfatal, remains a distressing aftermath for a few (6 per cent).

operations on the mitral valve doubly dangerous. In special cases where, in spite of these latter complications, the patient's life is being threatened by recurring pulmonary edema, a pulmonary-azygos shunt may offer a reasonable compromise. We have recently undertaken this successfully as an alternative in a patient with considerable aortic regurgitation.

A further attempt to classify patients into subgroups for assessment for surgery may ultimately prove useful, but at the moment it is somewhat unsatisfactory and controversial. For the present the general principles outlined above seem safest.

The high incidence of Aschoff bodies (up to 25 per cent) noted in biopsies of the atrial appendage has been a surprising finding and out of line with clinical evidence of rheumatic activity. In view of the scant evidence under these circumstances of clinical rheumatic activity and the absence of significant postoperative reactivation, there is need for a further critical review of these clinical-pathologic relationships and perhaps some modification in our present concepts of "activity."

In concluding this review, it is with awesome admiration that one recounts the remarkable progress of the past five years made by our surgical colleagues. In the face of the dramatic improvement after operation in these often desperately ill patients, the enthusiasm of the moment is understandable, and the desire to extend these possible benefits to those not yet in need of help is tempting, especially since they present to the surgeon more favorable operative risks. In this connection, however, it is timely to emphasize that mitral stenosis is not always a progressive lesion and patients with lesser degrees of deformity may attain a comfortable old age. The long term observations of Bland and Jones on 1000 children followed for 20 years after rheumatic fever reveal the development of mitral stenosis in 117 patients. Of this group during the two decades of follow-up, only 12 have progressed to a state of disabling pulmonary hypertension with acute pulmonary edema and hemorrhage (now mostly in the third decade). Encouraging also in the older age group (from 30 to 40) are the factual data of Grant on the after-history of 1000 soldiers invalided from the British Army after World War I with valvular heart disease. During the 10 year period of observation he found that in those with mitral stenosis:

"The prognosis in cases with signs of early stenosis is good and in them exercise tolerance is best and cardiac enlargement least; about half live uneventfully and unchanged, only a small proportion, about 5 per cent, develop auricular fibrillation and congestive failure, and about 10 per cent die within 10 years. In the presence of great cardiac enlargement and congestive failure the prognosis is bad, very few cases displaying these signs survive the 10 years; the average of life is four to five years."

Further data on the adult age groups by decades are needed and will soon be available, but for the moment a formidable operation upon the mitral valve had best be reserved for those in need of relief and the benefits to date justify the risk involved. On the contrary, for those with little or no disability the operation seems illogical and ill advised. The possible creation in this group of an uncertain element of regurgitation and the hazards of premature auricular fibrillation and embolism render the procedure unacceptable as a purely preventive measure. The ultimate solution for the majority of these patients is more subtle than the simple correction of a mechanical defect: their problem involves also a diseased myocardium, and their fate is inexorably linked with the vagaries of their rheumatic state.

Summary

The renewed interest in surgery for mitral stenosis is reviewed and the progress of the past five years summarized. The present status of the indirect operation (pulmonary-azygos shunt) is discussed, and the notable advances with the direct attack (finger-fracture valvuloplasty and commissurotomy) have been brought up to date (May 1951) by means of a survey of selected centers here and abroad.

Detailed information is available on 352 patients who have had an operation on the mitral valve. It is quite likely that the total now approaches 500 cases.

The over-all operative mortality has been 15 per cent. Post-operative embolism occurred in 6 per cent. Clinical improvement in the majority has been prompt and striking, and this has been fully supported by catheterization data. An appraisal of the more remote effects must await the passage of time.

Those most likely to benefit are patients under the age of 50 with only slight to moderate cardiac enlargement who are nevertheless seriously limited by pulmonary hypertension and congestion.

A formidable procedure of this magnitude should be reserved for those in trouble; it has no place in the management of patients with little or no disability.

REFERENCES

[1] ADAM, A.: Ueber die traumatischen Veranderungen gesunder Klappen des Herzens. Ztschr. f. Kreislaufforsch. **19:** 313, 1927.

[2] D'ALLAINES, F., LENÈGRE, J., DUBOST, C., MATHIVAT, A., AND SCÉBAT, L.: L'anastomose veine pulmonaire—veine azygos dans le rétrécissement mitral à propos d'un cas opéré avec succès. (1) Bull. et mém. soc. méd. hôp. Paris **65:** 512, 1949. (2) Arch. mal. coeur **42:** 456, 1949.

[3] —, —, —, SCÉBAT, L., AND MATHIVAT, M.: L'anastomose veineuse azygo-pulmonaire dans le traitement du rétrécissement mitral oedemateux. Cardiologia **15:** 266, 1949.

[4] ALLEN, D. S.: Intracardiac surgery. Arch. Surg. **8:** 317, 1924.

[5] —: Le traitement chirurgical de la stenose mitrale. Arch. franco-belges de chir. **28:** 394, 1925.

[6] —, AND GRAHAM, E. A.: Intracardiac surgery: a new method. J. A. M. A. **79:** 1028, 1922.

[7] ALROY, MICHAEL: Surgery of mitral disease. Lancet **1:** 1369, 1951.

[8] BAILEY, C. P.: The surgical treatment of mitral stenosis (mitral commissurotomy). Dis. Chest **15:** 377, 1949.

[9] BAILEY, C. P.: Personal communication, April 1951.

[10] BAKER, C., BROCK, R. C., AND CAMPBELL, M.: Valvulotomy for mitral stenosis. Report of six successful cases. Brit. M. J. **1:** 1283, 1950.

[11] BEDFORD, D. E., PAPP, C., AND PARKINSON, J.: Atrial septal defect. Brit. Heart J. **3:** 37, 1941.

[12] BERNHEIM, B. M.: Experimental surgery of mitral valve. Bull. Johns Hopkins Hosp. **20:** 107, 1909.

[13] BILLROTH, T., quoted from Jeger, E.: Die Chirurgie der Blutgefasse und des Herzens. Berlin, A. Hirschwald, 1913. P. 295.

[14] BLALOCK, A.: Personal communication from Dr. E. C. Andrus (Blalock, A. and Bing, R.), May 1951.

[15] BLAND, E. F., AND JONES, T. D.: Rheumatic fever and rheumatic heart disease: A twenty-year report on 100 patients followed since childhood. Circulation **4:** 836, 1951.

[16] —, AND SWEET, R. H.: A venous shunt for marked mitral stenosis. Mass. General Hospital, Case 53. Am. Pract. **2:** 756, 1948.

[17] —, AND —: A venous shunt for advanced mitral stenosis. J. A. M. A. **140:** 1259, 1949.

[18] BRANTIGAN, O. C.: Personal communication, July 1951.

[19] BROCK, R. C.: Personal communication from Baker, C., Brock, R. C., Campbell, M., and Wood, P., April 1951.

[20] BRUNTON, T. L.: Preliminary note on possibility of treating mitral stenosis by surgical methods. Lancet **1:** 352, 1902.

[21] COURNAND, A.: Some aspects of the pulmonary circulation in normal man and in chronic cardiopulmonary disease. Circulation **2:** 641, 1950.

[22] CUSHING, H., AND BRANCH, J. R. B.: Experimental and clinical notes on chronic valvular lesions in the dog and their possible relation to further surgery of the cardiac valves. J. M. Research **12:** 471, 1908.

[23] CUTLER, E. C., AND BECK, C. S.: Present status of surgical procedures in chronic valvular disease of heart: final report of all surgical cases. Arch. Surg. **18:** 403, 1929.

[24] —, AND LEVINE, S. A.: Cardiotomy and valvulotomy for mitral stenosis. Experimental observations and clinical notes concerning operated case with recovery. Boston M. & S. J. **188:** 1023, 1923.

[25] —, —, AND BECK, C. S.: Surgical treatment of mitral stenosis: experimental and clinical studies. Arch. Surg. **9:** 689, 1924.

[26] DEXTER, L., GORLIN, R., LEWIS, B. M., SPIEGL, R. J., AND HAYNES, F. W.: Physiological evaluation of patients with mitral stenosis before and after mitral valvuloplasty. Proceedings, 24th Scientific Session, Am. Heart Assoc., June 1951.

[27] DOW, J. W., AND DEXTER, L.: Circulatory dynamics in atrial septal defect. J. Clin. Investigation **29:** 809, 1950.

[28] DOYEN, E.: Chirurgie des malformations congenitales ou acquises du coeur. 26th Cong. de l'assoc. franc. de chir. Presse méd. **21:** 860, 1913.

[29] DRAPER, A. J., BING, R. J., FRIEDLICH, A., HEIMBECKER, R., AND DAMMANN, J. F.: Physiological studies in pre and postoperative mitral stenosis. J. Clin. Investigation **29:** 809, 1950.

[30] DURANT, T.: Cited by Bailey, C. P.: The surgical treatment of mitral stenosis. Dis. Chest. **15:** 377, 1949.

[31] EDITORIAL: Surgical operation for mitral stenosis. Lancet **1:** 461, 1902.

[32] FERGUSON, F. C., KOBILAC, R. E., AND DIETRICK, J. E.: Varices of bronchial veins as source of hemoptysis in mitral stenosis. Am. Heart J. **28:** 445, 1944.

[33] GLOVER, R. P., BAILEY, C. P., AND O'NEILL, T. J. E.: Surgery of stenotic valvular disease of the heart. J. A. M. A. **144:** 1049, 1950.

[34] —, O'NEILL, T. J. E., AND BAILEY, C. P.: Commissurotomy for mitral stenosis. Circulation **1:** 329, 1950.

[35] GORLIN, R., AND GORLIN, S. G.: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulation shunts. Am. Heart J. **41:** 1, 1951.

[36] —, HAYNES, F. W., GOODALE, W. T., SAWYER, C. G., DOW, J. W., AND DEXTER, L.: Studies of the circulatory dynamics in mitral stenosis. Am. Heart J. **41:** 30, 1951.

[37] GRANT, R. T.: After histories for ten years of a thousand men suffering from heart disease. Heart **6:** 275, 1933.

[38] HARKEN, D. E.: Personal communication, May 1951.

[39] —, ELLIS, L. B., DEXTER, L., FARRAND, R. E., DICKSON, J. F., III: The responsibility of the physician in the selection of patients with mitral stenosis for surgical treatment. Circulation. In press.

[40] —, —, WARE, P. F., AND NORMAN, L. R.: The surgical treatment of mitral stenosis. I. Valvuloplasty. New England J. Med. **239:** 801, 1948.

[41] JAROTZKY, A.: Zur Frage der Operation im Innern des Herzens bei Stenosis mitralis. Zentralbl. f. Chir. **53:** 140, 1926.

[42] KLEBS, F.: Ueber operative verletzungender Herzklappen und deren Folgen. Prag. Med. Wchnschr. **1:** 29, 1876.

[43] LENÈGRE, J.: Personal communication, April 1951.

[44] LONGMIRE, W. P.: Personal communication from Dr. W. H. Muller, Jr. (and W. P. Longmire), May 1951.

[45] LUTEMBACHER, R.: De la sténose mitrale avec communication interauriculaire. Arch. mal. coeur **9:** 237, 1916.

[46] MACCALLUM, W. G., AND MCCLURE, R. D.: On mechanical effects of experimental mitral stenosis and insufficiency. Bull. Johns Hopkins Hosp. **17:** 260, 1906.

[47] MURRAY, G.: Treatment of mitral valve stenosis by resection and replacement of valve under direct vision. Arch. Surg. **61:** 903, 1950.

[48] O'FARRELL, P. T.: The clinical diagnosis of congenital heart disease. Irish J. M. Sc. **153:** 608, 1938.

[49] PINCOFFS, M. C.: Discussion of "a venous shunt for mitral stenosis" (Bland-Sweet). Tr. Am. Clin. & Clim. Assoc. **48:** 77, 1948.

[50] POWERS, J. H.: The experimental production of mitral stenosis. Arch. Surg. **18:** 1945, 1929.

[51] —: Surgical treatment of mitral stenosis: an experimental study. Arch. Surg. **25:** 554, 1932.

[52] PRIBRAM, B. O.: Die operative Behandlung der Mitralstenose. Arch. f. klin. Chir. **142:** 458, 1926.

[53] SCHEPELMANN, E.: Versuche zur Herzchirurgie. Arch. f. klin. Chir. **95:** 739, 1912.

[54] SMITHY, H. G.: An approach to the surgical treatment of chronic valvular disease of the heart. Read before the 16th Annual Assembly, Southeastern Surg. Congress, April 1948.

[55] —, BOONE, J. A., AND STALLWORTH, J. M.: Surgical treatment of constrictive valvular disease of the heart. Surg. Gynec. & Obst. **90:** 175, 1950.

[56] —, AND PARKER, E. F.: Experimental aortic valvulotomy: preliminary report. Surg. Gynec. & Obst. **84:** 625, 1947.

[57] SOUTTAR, H. S.: Surgical treatment of mitral stenosis. Brit. M. J. **2:** 603, 1925.

[58] SWAN, H.: Mitral stenosis, an experimental study of pulmonary-azygos venous anastomosis. Am. Heart J. **38:** 367, 1949.

[59] SWEET, R. H., AND BLAND, E. F.: Surgical relief of congestion in the pulmonary circulation in cases of severe mitral stenosis. Ann. Surg. **130:** 384, 1949.

[60] TUFFIER, T.: Etat actuel de la chirurgie intrathoracique. Tr. Internat. Cong. Med. 1913, London, 1914; sect. 7, Surg. Part 2, p. 249, 1914.

ABSTRACTS

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BACTERIAL ENDOCARDITIS

Reynolds, R. W., Lev, M. W., and Weinshel, M.: Subacute Bacterial Endocarditis. Report of a Case with Recovery from Reinfection after Thirty-Two Months. Am. Heart J. **41**: 727 (May), 1951.

The authors present a case report in which there was recovery from a reinfection contracted 32 months after the initial episode of subacute bacterial endocarditis. The patient was a 62 year old white woman with rheumatic, hypertensive, and arteriosclerotic heart disease, and streptococcus viridans endocarditis. On the twentieth day, penicillin (50,000 units every three hours) was stopped in view of six consecutively negative blood cultures. Six days later the same organism was again isolated, and penicillin was resumed in larger doses (75,000 units every three hours), until discharge on the seventy-second hospital day. Thirty-two months later reinfection with the same organism occurred. Therapy with penicillin (300,000 units every 12 hours) was instituted. Recovery was without incident, and the patient was discharged "cured" on the fifty-fifth hospital day. Four weeks later the patient died suddenly of multiple and massive intracerebral hemorrhages. Necropsy examination revealed healed endocarditis and three true aneurysms of the mitral valve. The endocarditis played no role in the terminal episode. The authors stress the importance of early diagnosis, adequate dosage and prolonged therapy of subacute bacterial endocarditis. Inadequate therapy may lead to reactivation. A "cured" patient is considered to be just as susceptible to another infection as he would have been had only the antecedent rheumatic valvulitis been present.

HELLERSTEIN

Dowling, H. F., and Murray, F. J.: The Incidence and Cost of Treatment of Bacterial Endocarditis: A Study of All Cases Occurring in Metropolitan Washington in the Year 1948. Am. J. M. Sc. **221**: 612 (June), 1951.

A detailed survey of the occurrence of bacterial endocarditis in a large urban area disclosed a total of 33 patients, or an incidence of 2.4 per 100,000 in 1948. The diagnosis was based on clinical findings plus positive blood cultures in 26 patients, and at autopsy in seven others. The disease occurred more frequently in men than in women and slightly more in Negro than in white patients. There were 20 deaths in the entire group; however, of the 25 patients who received specific treatment only 12 died. The estimated period of disability among the survivors was 117 days per patient. During the period of treatment, the average amount of penicillin administered per patient was 178,020,000 units. The estimated cost to private patients for all expenses exclusive of physician's fees was $601.61.

Because of financial hardships encountered in the care of bacterial endocarditis, the authors suggest that state or local government agencies provide antibiotics and consultants for those patients who are unable to pay for them.

SHUMAN

BLOOD COAGULATION

Shapiro, S., and Weiner, M.: An Evaluation of Methods of Dicumarol Administration. Am. Heart J. **41**: 749 (May), 1951.

The authors discuss various schemes of dicumarol administration and present details of their intermittent dosage schedule and the more commonly used maintenance dose method. In estimating the

size of the initial dose, the following factors are important: weight, age, nutritional state, anemia, liver disease, initial prothrombin time, urgency of therapy, and past history of gastrointestinal disease. In the maintenance dose method an initial dose (300 mg. the first day, 200 mg. the second day) is followed by smaller daily amounts in an attempt to obtain and maintain a constant elevation of the prothrombin time within a safe range. Since dicumarol disappears from the plasma slowly, the authors believe that relatively infrequent doses are indicated. In their intermittent dosage schedule, a large single dose of dicumarol (200 to 1100 mg.) is given initially so that an adequate initial response is obtained. No further immediate dosage is given, and the prothrombin time is checked regularly. After the peak prothrombin response is passed in subsequent serial determinations, and when the prothrombin time is falling toward normal, another single effective dose is administered. This cycle is continued. There is no problem of accumulation. Failure of absorption can be recognized promptly. Patients who transform dicumarol rapidly may require doses as frequently as every two or three days, while "slow transformers" may require doses only at intervals of 10 days or more. An illustrative case is presented demonstrating the problems of accumulation and the superiority of the intermittent method over the daily maintenance method.

HELLERSTEIN

CONGENITAL ANOMALIES

Fishman, L., and Silverthorne, M. C.: Persistent Patent Ductus Arteriosus in the Aged. Am. Heart J. **41:** 762 (May), 1951.

The authors present case reports of two elderly women with persistent patent ductus arteriosus. The correct diagnosis was made ante mortem, and confirmed at autopsy in 1 case. The first patient, 75 years old, had enjoyed good health until two years before death, at which time evidence of congestive heart failure appeared. The second patient, 70 years old, is still living, and has responded to treatment for cardiac decompensation. The authors review the generally accepted indications for surgical intervention for complicated patent ductus arteriosus (bacterial endocarditis, congestive failure, retardation of physical growth and development). However, in uncomplicated patent ductus arteriosus, there is a division of thought between advocates of surgical and nonsurgical management. Reports of functional patent ductus arteriosus in elderly patients may help to clarify the prognostic significance and compatibility with long life of uncomplicated patent ductus arteriosus.

HELLERSTEIN

Lequime, J., Denolin, H., Göskel, F., Jonnart, F., and Wybauw, M.: The Circulation in Interauricular Communication. Arch. mal. coeur **44:** 539 (June), 1951.

The authors studied the dynamics of the circulation and respiration in eight subjects with typical clinical, radiologic and electrocardiographic signs of an interatrial septal defect. The age of the patients was between 8 and 42 years. None of them was cyanotic and all had a systolic murmur in the second left intercostal space, in some followed by a disastolic murmur. At x-ray examination, hypertrophy of the right ventricle, a prominent left middle arch and enlargement of the pulmonary arteries, and a small aortic knob were present in all cases. The electrocardiogram invariably revealed right bundle branch block.

By cardiac catheterization it was found that the flow in the pulmonary artery was markedly increased (7.34 to 20.2 liters per minute) in contrast to a relatively low systemic flow (2.59 to 6.66 liters per minute). In all cases a considerable shunt (4.75 to 16.12 liters per minute) from left to right auricle was calculated on the basis of elevation of the oxygen saturation in the latter chamber. In three cases there was probably in addition a less important interatrial shunt from right to left. At exercise, the utilization quotient of oxygen (O_2 consumption/pulmonary ventilation) increased as in normal persons. This observation can be used for the differential diagnosis of interatrial septal defect from other congenital malformations. Inhalation of pure oxygen was followed, after a normal delay, by maximal oxygen saturation of the arterial blood, thus indicating satisfactory pulmonary function.

The authors conclude that the existence of an arteriovenous interatrial shunt and the increase in pulmonary flow explain completely the characteristic findings of this malformation, namely, right ventricular hypertrophy and dilatation of the pulmonary artery and its branches.

PICK

Shumacker, H. B., Jr.: Suggestions Concerning the Use of the Subclavian Which Arises from the Aorta in the Treatment of Tetralogy of Fallot. Yale J. Biol. & Med. **23:** 486 (June), 1951.

The author describes three cases of tetralogy of Fallot, in one of which he transplanted the origin of the subclavian artery to a more suitable portion of the aorta after having performed an end to side subclavian–pulmonary artery anastomosis. The transplantation was performed because with the subclavian artery in its normal position, the anastomosis did not permit blood to pass through, since the vessel was flattened out against the relatively rigid aorta. With the vessel arising from the descending aorta, the anastomosis now pulsated vigorously.

In the other two cases an end to side subclavian–pulmonary artery anastomosis was accomplished,

but no blood passed through the connection except when the hilum of the lung was elevated in a cephalad direction. In order to maintain such a position, traction upward was made upon the cuff of hilar pleura and the adjacent vascular sheath. A sort of inverted T plastic closure of the defect in the hilum and mediastinum brought about a permanent cephalad elevation of the pulmonary artery and hence a release of the tension.

ABRAMSON

Carnegie, D. M.: Angiocardiography in Congenital Heart Disease. Brit. M. J. 4717: 1230 (June 2), 1951.

A large number of these cases of congenital heart disease are serious anesthetic risks. Angiocardiography should therefore be carried out in an x-ray theater with full surgical and anesthetic equipment to deal with any emergency. Preoperative cyanotic attacks are of bad prognostic significance. The older patients should be premedicated with Pentobarbitone and atropine, the younger with rectal Thiopentone and atropine. Quinidine and a test dose of Diodone should also be given preoperatively. Cyclopropane, ether and oxygen, through a cuffed endotracheal tube, form the anesthetic of choice. Intravenous procaine, both before and after the injection of Diodone, should be given through a large cannula inserted into the vein under direct vision. Serial blood pressures and electrocardiographic tracings ought to be recorded. The patient must be carefully watched for 15 minutes after the injection; must be under the care of the anesthetist until consciousness is regained; and must spend the first 3 to 12 postoperative hours in an oxygen tent.

BERNSTEIN

Botelho Reis, N., Medeiros, N., and Amorim, E.: The Heart in Sternal Depression. Arq. brasil. cardiol. **4:** 211 (June), 1951.

Thirteen cases of sternal depression were analyzed from the cardiovascular standpoint, including clinical, roentgenologic and electrocardiographic studies. Circulation time, venous pressure and vital capacity were also determined. According to the chest measurements, most patients showed a lesser degree of sternal depression than those previously described in the literature. The most frequently associated deformity was the so-called flat chest, which was observed in seven instances. The authors have followed the classification suggested by Evans, although, with the exception of the apparent increase in heart size in the funnel-shaped chest, the corresponding cardiac changes originally described could not be confirmed. Apical systolic murmurs and an accentuated or reduplicated second heart sound at the pulmonary area were the most frequent findings on auscultation. The main roentgenologic features are discussed and the high incidence of incomplete right bundle branch block is emphasized. According to the authors, the changes in shape and position of the heart as observed roentgenologically may be sufficiently characteristic to permit the correct diagnosis in most cases.

SCHLESINGER

Adams, H. D.: Congenital Arteriovenous and Cirsoid Aneurysms. Surg., Gynec. & Obst. **92:** 693 (June), 1951.

The author presents a study on 22 patients with congenital arteriovenous and cirsoid aneurysm located in different portions of the body. In most of the cases the development and the progression of the lesions was extremely slow. Locally, they exhibited palpable and often visible venous pulsation, a palpable thrill and an audible bruit continuous throughout the cardiac cycle. Other findings were the presence of an elevated venous pressure and an increased oxygen content of venous blood.

With regard to treatment, some cases of cirsoid aneurysms were handled by single- or multiple-stage local excision. In others simple ligation of the involved arterial trunk was carried out, but this was generally followed by recurrence in several months. The treatment of choice was considered to be complete surgical extirpation of the lesion.

ABRAMSON

Coelho, E., Da Fouseca, M., Pinto, R., and Nunes, A.: Pulmonary Stenosis with Large Interatrial Septum Defect and Severe Cyanosis. Cardiologia **18:** 183, 1951.

The authors report two cases of congenital pulmonic stenosis combined with a large interatrial septal defect, both diagnosed during life and proved by autopsy. The common diagnostic features were intense cyanosis, clubbing, polycythemia, a loud, systolic murmur in the second left intercostal space right ventricular hypertrophy and large P waves in the electrocardiogram, and enlargement of the pulmonary artery at fluoroscopy. The differential diagnosis against Fallot's tetralogy and Eisenmenger's complex was made by cardiac catheterization, during which the catheter could be passed into the left auricle; and by angiocardiography, which revealed early filling of the left ventricle and aorta, before visualization of the right ventricle and the pulmonary artery. The authors emphasize the importance of the correct diagnosis of this uncommon malformation in view of possible surgical correction. Recent experience has shown that valvulotomy may be very successful, while a Blalock operation proves insufficient to relieve the cyanosis and may, for hemodynamic reasons, even worsen the condition.

PICK

Stiefel, G. E.: The Prognosis of Untreated Congenital Malformations of the Heart and Big Vessels. Cardiologia **18:** 257 (Fasc. 5) 1951.

Among 7819 autopsies the author found 91 instances (1.16 per cent) of congenital cardiovascular malformations. More than half of the cases had coarctation of the aorta or an intraventricular septal defect, the other half consisted, in approximately equal numbers, of other more common types of congenital heart disease. There were about twice as many men as women.

The life expectancy is considerably reduced in the presence of congenital heart disease. An early critical phase of death is between birth and 2 years of age, during which time nature eliminates severely affected individuals who have reduced vitality. The occurrence of various types of serious complications at the beginning of puberty initiates a second period of selection. From then on the distribution curve of death in the various age groups assumes a normal pattern. From this analysis it would appear that the time between the third and the tenth year is the most suitable period for surgical intervention.

PICK

CONGESTIVE HEART FAILURE

Sherer, M. G., and Greer, W. E. R.: Cyclic Premenstrual Congestive Heart Failure. New England J. Med. **244:** 973 (June 28), 1951.

The case of a 37 year old woman with rheumatic heart disease, mitral stenosis and auricular fibrillation is presented. Signs and symptoms of congestive heart failure occurred in cyclic episodes associated with premenstrual fluid and electrolyte retention. The authors believe that premenstrual water and salt retention probably results from increased adrenocortical activity secondary to a rise in ACTH production consequent to pituitary gland stimulation by estrogen-oxidative products. They suggest that the condition should be treated with salt restriction, mercurial diuretics and cardiac glycosides. Hormonal therapy to depress pituitary stimulation during the premenstrual period may also be of benefit. Furthermore, they recommend that elective surgery in female patients with rheumatic heart be performed only during the middle of the intermenstrual phase of the cycle.

SAGALL

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Kupfer, S.: Can Experimental Shock Be Induced by Coronary Occlusion? Proc. Soc. Exper. Biol. & Med. **76:** 134 (Jan.), 1951.

The left ramus descendens anterior of the exposed hearts of dogs was ligated. Arrhythmias were prevented by the use of small doses of quinidine. Records of aortic, left atrial and right atrial pressures were repeatedly recorded by calibrated Gregg-type manometers for five to seven hours. Blood volume and cardiac output determinations were made in some animals. On the basis of an analysis of cardiac output, blood volume, and pressure pulses there was no evidence that ligation of a major coronary branch for a period up to seven hours causes circulatory failure of peripheral origin in dogs.

Comparison of cardiac output data obtained by the Fick method and the aortic pulse contour method showed sufficient disagreement to indicate that the latter method is not sufficiently accurate for quantitative evaluation of cardiac output, even when pressure pulses of normal contour and normal aortic pressures are present.

MINTZ

Papp, C., and Smith, K. S.: Prognosis and Treatment of Cardiac Infarction. Brit. M. J., **4721:** 1471 (June), 1951.

Two hundred consecutive cases of cardiac infarction, 175 treated on conservative lines and 25 treated with anticoagulants, were collected from consultant, general, and hospital practice and divided into three groups—slight, moderate, and severe. The prognostic significance of each of these groups was investigated separately and the clinical and electrocardiographic findings were correlated. The ages of the patients ranged from 34 to 75 years; the sex ratio was five men to one woman; the total mortality was 25 per cent, being about equal in the sexes.

More than half of the deaths occurred during or following first cardiac infarction. Death in 45 (90 per cent of the 50 who died) was due to further cardiac infarction, shock, or congestive heart failure; in only five was thromboembolism the cause, and then local thrombosis was more often responsible than embolism. The success of anticoagulant treatment is therefore due much less to prevention of embolism than to reduction of the thrombogenic effect of circulatory shock on the myocardium, lungs, and peripheral circulation. The choice of anticoagulant depends on the ready availability of laboratory control. The indications for additional treatment with penicillin, ouabain, quinidine, oxygen, and analgesics are discussed.

BERNSTEIN

ELECTROCARDIOGRAPHY

Horger, E. L., Dotter, C. T., and Steinberg, I.: Electrocardiographic Changes during Angiocardiography. Am. Heart J. **41:** 651 (May), 1951.

To explore a possible mechanism of death following angiocardiography, the authors studied the electrocardiographic changes in 16 patients undergoing angiocardiography. Continuous records were made during and following the rapid injection of Diodrast (70 per cent) or Neoiopax (75 per cent). There was an average increase in heart rate of 27.3 beats per minute. R-T segment depression and decrease in amplitude and inversion of the T wave

occurred approximately 10 seconds after injection. In the majority of cases changes in the T wave and R-T segment returned to their preinjection form in 60 seconds. The onset of the changes occurred after the lapse of time which would be required for the drug to reach the systemic arteries, including coronary arteries. In nine subjects auricular or ventricular premature contractions occurred. No abnormal rhythms developed. Because of the similarity of the electrocardiographic changes (tachycardia, flattening and inversion of T waves, depression of R-T segments) to those in acute coronary insufficiency, the authors believe that the contrast substance produces some change in the coronary circulation with resulting myocardial anoxia. In subjects with inadequate coronary circulation, it is possible that increased anoxia may account for sudden death.

HELLERSTEIN

Wolfram, J.: Bundle Branch Block without Significant Heart Disease. Am. Heart J. **41:** 656 (May), 1951.

The authors studied 52 patients with bundle branch block, and found that 63 per cent had no clinically evident cardiac disease. Of 35 patients with right bundle branch block, 26 (74 per cent) had no evidence of organic cardiac disease. Of 17 patients with left bundle branch block, seven (41 per cent) did not show evidence of organic heart disease. However, four of these seven patients had hypertension. The author concludes that in a considerable percentage of cases bundle branch block is not an expression of any clinically definable morbid anatomy or physiology. The danger of creating cardiac invaldism in otherwise essentially healthy persons with bundle branch block is emphasized.

HELLERSTEIN

Langendorf, R.: Aberrant Ventricular Conduction. Am. Heart J. **41:** 700 (May), 1951.

The author presents clinical examples demonstrating the mechanism of aberrant ventricular conduction of supraventricular impulses in patients with sinus rhythm, nodal rhythm, and auricular fibrillation. Aberrant ventricular conduction is more prone to occur if an impulse arises early in diastole of the preceding beat before recovery has been completed in all parts of the conducting tissue. Where such aberrant ventricular complexes occur in runs they may be mistaken for ventricular paroxysmal tachycardia, and the patient may be deprived of the benefit of digitalization. In the presence of auricular fibrillation or flutter, the lack of a "post-extrasystolic" pause, together with variations in coupling of the aberrant beat can be used as a guide in the differential diagnosis between aberration and ventricular premature systoles.

HELLERSTEIN

Scherf, D., Chick, F. B., Scharf, M. M., and Terranova, R.: Further Studies on Experimental Parasystole and Extrasystoles in Groups. Proc. Soc. Exper. Biol. & Med. **77:** 28 (May), 1951

In the atropinized heart under the influence of acetylcholine, typical parasystole was experimentally produced by electrical or mechanical stimulation of the dog's ventricle. All the characteristic signs of parasystole were present, such as changes in the length of coupling, protection of the ectopic center and combination beats. In these experiments extrasystoles with fixed coupling were not observed. Fixed coupling appeared readily after the topical application of barium, sodium chloride, digitalis or strophanthin. The authors conclude that in parasystole a special type of stimulus formation occurs and that the heart exhibiting a parasystolic stimulus formation need not show an extrasystolic one.

MINTZ

Israel, E.: Effect of Exercise (Master Double "Two Steps" Test) on the Electrocardiogram of Normal People. Israel M. J., **10:** 122 (May-June), 1951.

The author performed a double "two step" test following the technic of Master in 220 normal adults ranging from under 17 years to 40 years; most were between 17 and 30. He noted P-wave changes mostly in CF_4. The P-R interval was prolonged in one case only. The QRS complex did not change significantly. Nineteen cases showed significant S-T depressions (18 were in the age group under 22 years). Three cases showed S-T elevations. T-wave changes occurred in a few cases but the author feels that they were partly due to tachycardia, partly to autonomic nervous system effects, hyperventilation, posture, etc., rather than anoxia or myocardial damage. The Q-T intervals were normal.

The author suggests that the length of time the changes persist should be further studied as a possibly valuable criterion of significant change. He feels that some of these changes may be related to myocardial damage resulting from acute infectious disease, since some of the positive tests were negative when repeated a few weeks later.

BERNSTEIN

Gillman, H.: Various Geometric Relations between the Frontal Vectordiagram and the Unipolar Extremity Leads. Ztschr. f. Kreislaufforsch. **40:** 355 (June), 1951.

The author presents mathematical proof that both the standard and the unipolar limb leads are derived from the frontal vectordiagram. Consequently, unipolar limb leads cannot give additional information concerning electrophysiologic events in the heart and cannot be associated with specific parts of the heart. However, since the reference system of the unipolar limb leads is shifted by 30

degrees against Einthoven's triangle, certain vectors may be reflected better in the latter leads than in the standard limb leads. This applies especially to vectors which are parallel to a line connecting the center of the heart with an extremity.

PICK

Segers, M.: The Alternans of Atrioventricular Conduction Time. Arch. mal. coeur **44:** 525 (June), 1951

The author presents a new example of alternation in the length of the P-R interval. The electrocardiogram was obtained from a 68 year old sclerotic patient, who, in addition to right bundle branch block, had 2:1 A-V block persisting over a long period of observation. The P-R intervals showed alternation between 0.14 and 0.21 second and later between 0.14 and 0.30 second. The author believes that this represents a true instance of alternans of A-V conduction to which the conventional classification of second degree A-V block—type I (Wenckebach) and type II (Mobitz)—would not apply. An analogous phenomenon, namely alternation of intraventricular conduction, was observed previously in cases of intermittent bundle branch block.

PICK

Segers, M.: Inconstant Intraventricular Block. Acta Cardiol. **6:** 272 (Fasc. 3), 1951.

The author discusses the significance of various types of intermittent and transient intraventricular block. Examples are presented of aberrant intraventricular conduction associated with auricular premature contractions or occurring in auricular fibrillation with variations of the cycle length. Several instances of intraventricular block are shown where paradoxic shortening of QRS was seen with a premature beat. This phenomenon is explained by the author as a manifestation of a supernormal phase of recovery of the intraventricular conduction system. Independent variations of atrioventricular and intraventricular conduction may occur, and are illustrated in an instance of alternation of the length of P-R and QRS duration.

The author believes that there is no fundamental difference in the clinical significance of permanent and transient intraventricular block. The appearance of any type of conduction defect in the electrocardiogram indicates involvement of the myocardium by the underlying disease, and its disappearance predicates improvement or healing of the myocardial process. Intermittent types of intraventricular block appearing with increase of the heart rate frequently represent a preliminary stage of permanent block. Aberrant intraventricular conduction occurring with auricular arrhythmias may be considered benign in character if, in the course of an exercise test, the QRS duration of the normal sinus beats remains unchanged.

PICK

Schenetten, F. P. N.: Electrocardiographic Alterations in Dystrophy. Cardiologia **18:** 279 (Fasc. 5), 1951.

In 238 cases of malnutrition, with or without edema or with signs of "lipophil dystrophy," the following electrocardiographic alterations were found: low voltage in the limb leads was present in 74 per cent of hospitalized cases and in 54 per cent of the ambulatory patients; a relative shortening of the P-Q interval was seen, especially in cases with bradycardia, while delay of conduction was found only exceptionally; the S-T segment in the precordial leads was distorted ("saddle form") and distinct U waves were frequent. Low T waves in association with low QRS complexes in both limb and precordial leads indicated a bad prognosis. Necropsy was performed on some cases with an electrocardiogram of the latter type; they revealed degenerative changes in the myocardium and in the epicardial fat tissue.

PICK

Braun, K., Fryd, C. H., and Liban, E.: Electrocardiographic Changes in Hypopotassemia Complicated by Pericarditis. Cardiologia **18:** 244, 1951.

The authors report electrocardiographic observations in a 20 year old man with hypopotassemia which developed in the course of chronic diarrhea of unknown etiology. During his first hospital admission, the electrocardiogram showed characteristic abnormalities of potassium deficiency (prolongation of the electric systole and marked U waves). On his second admission, the electrocardiogram showed elevation of S-T in leads I, II and aV_F as well as in the precordial leads, suggesting pericarditis. With further fall of the blood potassium to 5 mg. per 100 cc., marked U waves became recognizable, and later there was S-T depression and prolongation of the electric systole. The postmortem examination confirmed the diagnosis of pericarditis. The myocardium showed leucocytic infiltration and necrosis of muscle fibers in a few areas.

The authors assume that during the second admission of the patient, at the time of the lower potassium levels in the blood, subepicardial injury due to pericarditis had a more pronounced effect upon the electrocardiogram than the subendocardial injury due to hypopotassemia. This is in accordance with animal experiments in which it has been demonstrated that the effects of surface injury may completely mask those of damage of deeper subendocardial layers.

PICK

HYPERTENSION

Doumer, E., Lorriaux, A., and Steenhouwer, B.: Arterial Hypertension Due to Aplasia of the Left Renal Artery with Malformation of the Ab-

dominal Aorta. Transient Effect of Nephrectomy. Arch. mal. coeur **44:** 446 (May), 1951.

The authors report a case of 40 year old man who had intermittent claudication for 10 years and hypertension (250/130) for two years. An intravenous pyelogram showed no excretion by the left kidney. Injection of the aorta with contrast material revealed complete obstruction of the aorta at the level of L_2 and no injection of the left renal artery and of the left kidney. After surgical removal of the left kidney the blood pressure fell transiently to normal values but returned to almost preoperative values within three months. Examination of the extirpated kidney revealed that it was supplied by two anomalous vessels of small caliber. Microscopically its parenchyma showed signs of nephritis of more recent origin.

PICK

Barrow, J. G., and Sikes, C. R.: The Use of Purified Veratrum Viride Alkaloids in the Treatment of Essential Hypertension. Am. Heart J. **41:** 742 (May), 1951.

The authors treated 25 hypertensive patients with Anatensol, a purified extract containing two alkaloids of veratrum viride. After a control period of two to six months, drug treatment was started, and the patients were seen at weekly intervals. In five patients, a significant drop in blood pressure (20 mm. Hg systolic and 10 mm. Hg diastolic) was produced by daily doses from 3 to 8 mg. In 12 patients, no hypotensive effect was produced by 2 to 6 mg. each day. Attempts to increase the daily dose were unsuccessful because of the appearance of nausea and vomiting. In eight patients, adequate therapeutic trial was precluded by the immediate or early onset of distressing gastrointestinal side effects. Doses as little as 0.5 to 1.0 mg. per day could not be tolerated. Atropine and Dramamine did not prevent or relieve the nausea. Tachyphylaxis developed in several patients, at a variable rate. In view of the relative ineffectiveness of noxious alkaloids of veratrum viride, the authors decry the widespread recommendation and use of these products.

HELLERSTEIN

Lee, R. E., and Holze, E. A.: Peripheral Vascular Hemodynamics in the Bulbar Conjunctiva of Subjects with Hypertensive Vascular Disease. J. Clin. Investigation. **30:** 539 (June), 1951.

The blood vessels of the bulbar conjunctiva of 15 hypertensive subjects was examined with a slit-lamp microscope and compared to normotensives. A pattern of peripheral vascular abnormalities in hypertension was found, although no single feature could be correlated absolutely with the degree of blood pressure, symptomatology, or duration of hypertension. The over-all picture featured narrowing of the terminal arterioles, augmented spontaneous vasomotor activity, and frequent elongation, coiling, and tortuosity of the capillaries. In addition, a heightened sensitivity of the metarterioles and precapillaries to topical epinephrine was noted. These latter conditions also obtained in four normotensive subjects who had had a spontaneous remission of previous hypertension.

WAIFE

Gropper, A. L., Surtshin, A., and Hedrick, J. T.: Effects of Veriloid on Essential Hypertension. Arch. Int. Med. **87:** 789 (June), 1951.

Veriloid, a proprietary preparation derived from veratrum viride, was employed for periods up to 180 days in the treatment of 35 patients with varying degrees of arterial hypertension. Rapidly dissolving and enteric-coated tablets were used; slowly dissolving tablets, now on the market, were not available. In the hospital, treatment with the drug appeared to cause lowering of the average diastolic pressure of 15 mm. Hg or more in 12 patients; in the outpatient department six were similarly affected. In nine patients the average diastolic pressure was maintained below 100 mm. Hg and in two below 90 mm. Acute but transient falls in blood pressure were seen frequently. No regression of the structural damage due to hypertension was noted.

BERNSTEIN

PATHOLOGIC PHYSIOLOGY

Bernthal, T., Green, W., Jr., and Revzin, A. M.: Role of Carotid Chemoreceptors in Hypoxic Cardiac Acceleration. Proc. Soc. Exper. Biol. & Med. **76:** 121 (Jan.), 1951.

Changes in heart rate were recorded during the application of hypoxic stimuli limited to the carotid chemoreceptors. The direct reflex change in heart rate initiated by hypoxia at the carotid chemoreceptors was a slowing of moderate degree. The authors concluded that the cardiac acceleration of generalized hypoxia does not depend upon the carotid chemoreceptors, although effects secondary to chemoreflex hyperpnea may contribute in a minor degree. The same conclusion probably holds true for the aortic chemoreceptors, since all known aspects of their function are qualitatively like those of the carotid bodies.

MINTZ

Carlson, R. F., Charbon, B. C., Charbon, H. G. A., and Adams, W. E.: The Effect of Decreasing the Amount of Lung Tissue on the Right Ventricular Pressures in Animals. J. Thoracic Surg. **21:** 621 (June), 1951.

The authors studied the effect of pneumonectomy, lobectomy or bilobectomy on the right ventricular pressure in a series of normal dogs under general anesthesia. The lung tissue was eventually reduced

to one or two lobes by three operations several months apart.

Following pneumonectomy, there was a rise in systolic blood pressure averaging 10 mm. Hg, with little change occurring in the diastolic pressure. Removal of the right lower and accessory lobes in animals previously subjected to pneumonectomy produced an average rise of 25 mm. Hg in systolic pressure and again no alteration in diastolic pressure. When the left lower lobe was subsequently removed in some of these animals, another rise in systolic blood pressure occurred.

Although many dogs tolerated extirpation of the right middle and upper lobes, very few survived removal of all pulmonary tissue except the left upper lobe. It was concluded that the right ventricle in dogs has considerable power of compensation provided the stress is imposed gradually.

ABRAMSON

Burdette, W. J.: Studies on the Metabolism of Cardiac Muscle from Animals in Shock. Yale J. Biol. & Med. **23:** 505 (June), 1951.

Shock was induced in fasted rats by bleeding or (in most cases) by constricting the hind limbs and later releasing the tourniquets. Metabolic changes were studied in slices of heart tissue. It was found that the glycogen content of cardiac muscle was reduced in traumatic shock, and the pyruvic acid content was increased. It was considered probable that these changes were associated with the accompanying anoxia.

Reduction of the potassium concentration in the medium to offset the elevation of potassium late in shock did not prevent the effect of shock in lowering oxygen consumption. It is therefore not likely that the lowered oxygen consumption in shock is due to hyperpotassemia.

ENSELBERG

Berlin, N. I., Rowles, D. F., Hyde, G. M., Parsons, R. J., Samson, P. C., and Port, S.: The Blood and Blood Turnover in Thoracic Surgery as Determined by P^{32} Labelled Red Blood Cells. Surg., Gynec. & Obst. **92:** 712 (June), 1951.

Using red blood cells labeled with P^{32}, the authors studied the blood volume changes in 27 patients two to six days after thoracic surgery. In the first stage thoracoplasty procedures the blood volume loss was found to vary from 840 to 1500 cc. During resection surgery, blood volume loss was even greater, in some instances rising to as high as 5,090 cc.

Because of this fact and since the hematocrit does not give an accurate indication of the blood volume, it was concluded that repeated direct measurements are necessary in thoracic surgery for optimum preoperative and postoperative management.

ABRAMSON

Bing, R. J., and Daley, R.: Behavior of the Myocardium in Health and Disease as Studied by Coronary Sinus Catheterization. Am. J. Med. **10:** 711 (June), 1951.

The myocardium of normal man at rest extracts appreciably more oxygen than other organs so far tested. The oxygen content of coronary venous blood varies from 4 to 7 volumes per cent with an average oxygen extraction of 12 volumes per cent. The normal left ventricular coronary flow is 65 cc. per minute for every 100 Gm. of myocardium. The oxygen consumption for the same unit of muscle averages 7.8 cc. per minute. At rest 5 to 8 per cent of the cardiac output is delivered to the heart.

In anemic patients increased oxygen extraction is one adaptive mechanism. In severe chronic anemia the cardiac output and the coronary flow are increased. Anoxia may act as a potent vasodilator and there is a correlation between cardiac output and coronary blood flow which is independent of variation in systemic arterial pressure. However, the coronary flow may not always be adequate to meet the metabolic demands of the myocardium in anemia.

The oxidative metabolism of the heart per unit weight is normal in the hyperkinetic state resulting from thyrotoxicosis, resembling the hypertrophied heart of essential hypertension. Thyroxin apparently does not increase the unit oxygen consumption of the myocardium, but only the total oxygen consumption by virtue of increased myocardial mass.

Cardiac hypertrophy resulting from essential hypertension is not accompanied by any significant increase in coronary blood flow or oxygen consumption per 100 Gm. of muscle. The arteriovenous oxygen difference remains normal. The total ventricular oxygen consumption and coronary flow must be increased, but cannot be assessed in hypertrophied hearts. The normal coronary flow per unit of myocardium in hypertension implies that the coronary vascular resistance shares in the generally increased arterial resistance. In coarctation of the aorta, on the other hand, the coronary A-V oxygen difference, the left ventricular coronary flow, and the oxygen consumption per 100 Gm. are increased. This may be caused by the absence of generalized elevation of the peripheral vascular resistance.

In heart disease due to arteriosclerosis, mitral or aortic valvular disease, the coronary blood flow per unit of myocardium is normal; the oxygen extraction a little above normal; and the oxygen consumption slightly increased. The coronary vascular resistance in cardiac failure is normal although an increase in the over-all resistance has been found. The coefficient of oxygen utilization of the myocardium is normally 60 per cent, but can increase during failure to 90 per cent. The carbohydrate metabolism of the failing heart appears to be normal.

Strophanthus preparations increase the cardiac output of the failing heart but do not significantly alter the coronary flow, the coronary arteriolar resistance, or the A-V oxygen difference. The heart apparently becomes more efficient by developing greater facility either in transferring oxidative energy into mechanical work or in the utilization of energy.

HARRIS

Harvey, R. M., Ferrer, M. I., Richards, D. W., Jr., and Cournand, A.: Influence of Chronic Pulmonary Disease on the Heart and Circulation. Am. J. Med. **10**: 719 (June), 1951.

Cardiopulmonary function studies in 48 patients with chronic pulmonary disease disclosed pulmonary arterial hypertension in 39 cases at rest. In chronic pulmonary emphysema most of the circulatory alterations—pulmonary hypertension, high cardiac output, and hypervolemia—stem from anoxia. The reversible nature of these changes indicates the importance of therapy. Optimal treatment includes antibiotics for relief of pulmonary infection, liberal use of atomized bronchodilators for the relief of bronchiolar obstruction and reduction of bronchial secretions, digitalis to improve right ventricular myocardial function, and phlebotomy to reduce hypervolemia. Oxygen therapy is beneficial but it should not be used continuously for fear of development of carbon dioxide narcosis.

In patients with silicosis and emphysema, pulmonary hypertension is less likely to be reversible, since it stems from anatomic alterations in the pulmonary vascular bed. Physical exertion should be curtailed to minimize right heart strain. The circulatory changes in patients with diffusion fibrosis probably spring from the anatomic lesions produced by the disease processes themselves rather than anoxia.

Cardiac failure in patients with chronic cor pulmonale and emphysema is generally characterized by high cardiac output. In patients with silicosis such failure is not always of the high output type. Measurement of arterial blood oxygen, carbon dioxide content, blood volume, and hematocrit may serve as indicators of the expected circulatory changes in chronic cor pulmonale.

HARRIS

Wisham, L. H., Yalow, R. S., and Freund, A. J.: Consistency of Clearance of Radioactive Sodium from Human Muscle. Am. Heart J. **41**: 810 (June), 1951.

The authors determined the clearance rate of radiosodium from the gastrocnemius and biceps muscles of normal subjects at rest, during moderate exercise, following fatiguing exercise, and during postural changes, over a period of up to three months. In every experiment, isotonic sodium chloride solution containing between one and four microcuries of radioactive sodium (Na^{24}) was injected into the belly of the muscle and immediately afterward a thin, mica window Geiger counter was placed in a fixed position over the injection site.

The rate of clearance at rest in the various subjects remained constant within a relatively narrow range over long time periods. On both moderate and fatiguing exercise, it increased more than 100 per cent within 30 seconds, while with postural changes no significant effect was noted.

It was concluded that the method of clearance of radioactive sodium from muscles could be used as a measure of gross changes of blood flow over a considerable period of time.

ABRAMSON

PATHOLOGY

Smith, J. M.: Primary (Atypical) Localized Amyloidosis of Heart: Case Report. U. S. A. F. M. J. **2**: 723 (May), 1951.

The authors report a case of primary localized amyloidosis of the heart in a 36 year old white man. They point out that amyloid disease of the heart is classified as: (1) primary (atypical) localized amyloidosis of the heart, in which amyloid deposition is confined to the heart with little or no involvement of other organs; (2) primary systemic amyloidosis, in which amyloid deposition in the heart is part of a generalized involvement of striated and smooth muscle and connective tissue; and (3) secondary (typical) amyloidosis, in which the characteristic involvement of the liver, spleen, kidneys, and adrenals is occasionally associated with amyloid deposition in the heart.

The most constant clinical feature observed in amyloidosis of the heart is intractable congestive heart failure. The electrocardiographic findings in primary amyloidosis of the heart vary and are not diagnostic; they may be indistinguishable from those seen in cases of myocardial infarction. The heart is usually slightly to moderately enlarged. A fairly frequent clinical finding of diagnostic value in the systemic type of primary amyloidosis is an associated macroglossia. Primary amyloidosis of the heart should be considered in all cases presenting the features of intractable congestive heart failure, moderate cardiac hypertrophy, definite but nonspecific electrocardiographic changes, and the absence of a history of hypertension, arteriosclerosis, or valvular heart disease.

BERNSTEIN

Dreyer, V.: Generalized Scleroderma with Pulmonary Fibrosis. Nord. Med. **45**: 734 (May), 1951.

Some typical symptoms of generalized scleroderma were found in a 53 year old woman. The initial symptoms, which appeared at the age of 37, were explained as rheumatoid arthritis and later as Raynaud's disease. Besides the sclerosis of the skin,

especially localized to the fingers and the face, there was difficulty in swallowing. The x-ray examination showed signs of sclerosis of the esophagus, and a biopsy from the gullet disclosed non-specific inflammation and an increased amount of collagen fibrils. Decreased function of the thyroid and suprarenal glands was also found. In the course of the disease there were several periods of fever, coughing and dyspnea. The x-ray examination revealed transient infiltrations with varying localization throughout the lungs and, finally, a permanent pulmonary fibrosis.

At no time were tubercle bacilli found in gastric washings; and bronchography failed to demonstrate bronchostenosis or bronchiectasia.

AUTHOR

Gancher, R.: Cardiac Enlargement and Failure, with Endocardial Fibrosis: A Case Report. Connecticut M. J. **15:** 379 (May), 1951.

A case is presented of unexplained cardiac hypertrophy and dilatation in a young man, with progressive cardiac decompensation and multiple visceral infarction. The significant pathologic findings were cardiac hypertrophy and dilatation, and a markedly thickened endocardium with adherent mural thrombi. There was no evidence of significant valvular disease, coronary artery disease or of myocarditis.

The pertinent literature is reviewed and a similarity indicated. Similarity to cases of congenital idiopathic hypertrophy in children is also shown, especially in view of the presence of marked endocardial fibrosis and thickening in some of the latter.

BERNSTEIN

Lyon, E.: Myocardosis in Infectious Hepatitis. Israel M. J. **10:** 139 (May–June), 1951.

Myocardosis is the term applied by the author to what has previously been referred to as "parenchymatous degeneration" of the cardiac muscle. The heart muscle is frequently secondarily involved by a primary liver affection which causes a disturbed protein metabolism, and its severity roughly parallels the drop in plasma proteins, especially the albumin.

The diagnosis of myocardosis is made from the electrocardiogram on the lengthening of the Q-T interval, shortening of the interval Q to second heart sound, P-R delay, QRS, S-T segment and T-wave changes.

Myocardosis is not of primary clinical significance, representing but a secondary metabolic disturbance. It is mostly reversible. It may be irreversible in chronic hepatitis and in posthepatitis cirrhosis.

The therapy of myocardosis is identical with the treatment of infectious hepatitis itself, mainly aiming at the restitution of euproteinemia (protein in the diet, plasma transfusion).

BERNSTEIN

Friedman, E. W., and Weiner, R. S.: Estimation of Hepatic Sinusoid Pressure by Means of Venous Catheters and Estimation of Portal Pressure by Hepatic Vein Catheterization. Am. J. Physiol. **165:** 527 (June), 1951.

The authors used a technic similar to that employed by Dexter for the lung. In dogs an end-hole catheter was wedged into a division of the hepatic vein and another into a division of the portal vein. Pressure in the sinusoids is measured by the direct connection between the catheter tip and the sinusoid bed by way of a static column of blood. When an afferent vessel to a capillary network is obstructed by a wedged catheter there is a drop in pressure distal to the blocked point. In an efferent vessel pressure is elevated proximal to the tip of the wedged catheter. Provided the vessels are of the same size, the average of the afferent pressures gives the sinusoid or capillary pressures. Sinusoid pressure measured 11.5 cm. of water; average portal pressure was 13.0 cm. of water. Pressures by "occlusive catheterization" of a hepatic vein were consistently higher by a few centimeters of water than those in the free portal vein. It is suggested that estimates of portal vein pressure may be obtained in intact subjects by means of a catheter with a single terminal opening wedged into a hepatic vein tributary.

OPPENHEIMER

Hejtmancik, M. R., Bradfield, J. Y., Jr., and Herrmann, G. R.: Acromegaly and the Heart: A Clinical and Pathologic Study. Ann. Int. Med. **34:** 1445 (June), 1951.

In this report are described the cardiovascular findings in 21 patients with acromegaly. Necropsies were performed in four subjects. Thirteen of the patients had evidences of heart disease. Five were in frank cardiac decompensation and two had transient episodes of left ventricular failure. Nine of 15 patients with electrocardiographic studies showed abnormal tracings, with impaired intraventricular conduction in six and left ventricular hypertrophy pattern in two. Six patients had hypertension, four had elevated basal metabolic rates, and five had diabetes mellitus. Pathologic study of four patients demonstrated cardiac enlargement. The heart in one case weighed 1,140 Gm. Microscopic sections showed hypertrophy of the myocardial fibers, with conspicuous diffuse fibrous tissue proliferation in two cases. Direct effect of the hormone of the anterior pituitary seems to be the predominant factor causal of cardiac hypertrophy and interstitial fibrous tissue proliferation. Increased work demand by other tissues stimulated to abnormal growth by hormonal action is contributory, as is occasionally thyrotoxicosis and/or impaired glucose metabolism. The integration of sporadic hypertension in the disease process, and the part it plays in the pathogenesis of cardiopathy, demand further evaluation. Hypertension

appears poorly tolerated by the heart of the acromegalic.

WENDKOS

Merkel, H., and Nadolny, G.: The Relationship of the Muscle Masses of Right and Left Ventricle. Ztschr. f. Kreislaufforsch. **40:** 341 (June), 1951.

In 52 cases of essential hypertension, with heart enlargement found at necropsy, the authors determined the weight of the whole heart, of the isolated right and left ventricle, and of the intraventricular septum. They found hypertrophy restricted to the left ventricle in 36 instances and a secondary hypertrophy of the right ventricle in 16 instances. In the majority of cases the increase of the muscle masses of the left ventricle was not uniform in that the free wall and septum showed different degrees of hypertrophy. In secondary hypertrophy of the right heart its weight was maximally double its normal weight. In five cases in which the weight of the right ventricle exceeded the normal value, histologic examination of the lungs did not reveal sufficient changes to account for the marked right ventricular hypertrophy. For these cases the authors assume combined essential hypertension in both the systemic and pulmonary circulation.

PICK

Levine, E., Stein, M., Gordon, G., and Mitchell, N.: Chronic Dissecting Aneurysm of the Aorta Resembling Chronic Rheumatic Heart Disease. New England J. Med. **244:** 902 (June 14), 1951.

Two patients with chronic dissecting aneurysm of the aorta are described. Their ages were 21 and 38 years. Both patients displayed cardiac enlargement, aortic systolic and diastolic murmurs, a wide pulse pressure, and recurrent, severe congestive cardiac failure. The clinical diagnosis in each instance was chronic rheumatic heart disease with aortic valvular involvement. The typical chest pain of dissecting aneurysm of the aorta did not occur in one case and in the other it was late in its appearance, apparently associated with recurrent dissection.

ROSENBAUM

Lenègre, J., Chevalier, H., and Jaquot, R.: Histologic Study of the Septum in Right Bundle Branch Block. Arch. mal. coeur **44:** 481 (June), 1951.

In seven cases with the electrocardiographic pattern of right bundle branch block, microscopic examination of the intraventricular septum and the conduction system according to the method developed by the authors revealed the following findings: In two cases with the "rare" type and in one case with "S" type of bundle branch block complete interruption of the right bundle and no lesion in the left bundle; in one case of intermittent right bundle branch block only slight hyperemic changes in the right main bundle branch without tissue destruction; in three cases of incomplete right bundle branch block (QRS < 0.12) the right bundle was completely intact. All seven cases showed marked right ventricular hypertrophy.

From these findings, the author concludes that a common etiologic factor in the pathogenesis of right bundle branch blocks of all types is right ventricular hypertrophy. The electrocardiographic pattern of complete and permanent block is invariably due to an anatomic interruption of the right bundle. A pattern of incomplete right bundle branch suggests right ventricular hypertrophy which may be associated with a destructive lesion in the conduction system of the right ventricle. The possible role of ventricular hypertrophy in the production of bundle branch lesions remains a matter for further investigations.

PICK

Siperstein, M. D., Chaikoff, I. L., and Chernick, S. S.: Significance of Endogenous Cholesterol in Arteriosclerosis: Synthesis in Arterial Tissue. Science **113:** 747 (June 29), 1951.

The aortas of chickens were incubated with C^{14}-labeled acetate. It was found that arteries can convert considerable quantities of acetate to carbon dioxide. Furthermore, aortas of rabbits and chickens showed a small but consistent ability to synthesize cholesterol. The ability to synthesize cholesterol in the arteries was about one fourth that observed with liver slices.

These and other experiments show that an artery cannot be considered totally passive. Arterial tissue metabolism is not restricted to catabolic processes. It also participates in reactions synthesizing phospholipids and, as shown here, in the conversion of acetate to cholesterol.

The result of this and other similar experiments indicates that endogenous cholesterol, originating within the artery itself and elsewhere in the body, may be of great importance in the pathogenesis of spontaneous arteriosclerosis.

WAIFE

Mendelson, C. L.: Acute Isolated Myocarditis in Pregnancy. Am. J. Obst. & Gynec. **61:** 1341 (June), 1951.

The clinical and autopsy findings in two cases of acute isolated myocarditis in pregnancy are presented. Both patients developed signs of congestive heart failure in the absence of previously known cardiac disease. Tachycardia and dyspnea were of marked degree, although only mild temperature elevations were noted. A significant reduction in blood pressure occurred. Impairment of myocardial function at the height of the physiologic circulatory load associated with pregnancy resulted in fatal cardiac decompensation in both instances.

At autopsy, the hearts were enlarged. There were

diffuse and focal infiltrations of the myocardium with mononuclear and polymorphonuclear cells. The muscle cells showed areas of degeneration and vacuolization. In one case, the right auricle contained an organized thrombus but otherwise no endocardial abnormalities were noted.

The author agrees with Gouley, McMillan and Bellet in stating that "Fiedler's myocarditis" is simply a general term applied to such cases and the etiology is obscure.

SHUMAN

Whitfield, A. G. W., and Birm, M. D.: "Myocarditis" and Aortic Hypoplasia in Arachnodactyly. Lancet **1**: 1387 (June), 1951.

A case of arachnodactyly is described in which death took place from "myocarditis." Hypoplasia of the aorta and organ hyperplasia were found at necropsy as well.

The clinical picture in this case was that of an extremely severe myocardial insufficiency for which no cause was apparent other than arachnodactyly, whose association with various congenital and acquired abnormalities of the cardiovascular system is well known.

Histological examination amply confirmed the "myocarditis," without abnormality of the coronary arteries.

BERNSTEIN

Kartagener, V. M.: Buerger's Disease and Lupus Erythematosus—A Chronic Form of the Libman-Sacks Syndrome? Cardiologia **18**: 225, 1951.

Two cases of a combination of Buerger's disease with chronic lupus erythematosus are reported. The association between endarteritis of a "rheumatic type" and chronic lupus erythematosus is likened to that between atypical verrucous endocarditis, with syndromes of periarteritis nodosa in the subcutaneous arterioles and disseminated lupus erythematosus. These conditions are regarded as a chronic form of the Libman-Sacks syndrome, where in the ratio of virulence to resistence is reduced.

BERNSTEIN

PHARMACOLOGY

Borison, H. L., and Wang, S. C.: Locus of the Central Emetic Action of Cardiac Glycosides. Proc. Soc. Exper. Biol. & Med. **76**: 335 (Feb.), 1951.

Experiments on dogs have revealed the existence of a chemoreceptor trigger zone for emesis which is quite distinct from the vomiting center. This zone is a bilateral structure situated at the surface of the medulla oblongata in the dorsal region of the area cinerea. Destruction of the emetic chemoreceptor zone renders animals permanently refractory to apomorphine given by vein, but it does not impair the vomiting response to orally administered copper sulfate. Eight out of nine such dogs failed to vomit when tested intravenously with known emetic doses of the cardiac glycosides, lanatoside C, scillaren A and ouabain.

The present delimitation of the central locus of emetic action of the cardiac glycosides by no means excludes the possibility that reflex vomiting may be initiated at certain peripheral sites by these drugs. A delayed emetic response to intravenous scillaren A was observed in one successfully operated dog suggests that there may be a site of emetic action for the cardiac glycosides other than in the medulla.

MINTZ

Moisset de Espanes, E.: The Effect of Acetylcholine and of Adrenaline on the Excitability of the Heart. Compt. rend. Soc. biol. **145**: 452 (March), 1951.

In order to study the effect of acetylcholine and epinephrine upon the fundamental properties of the excised frog heart, the authors used a special stimulator which permits independent variation of the intensity, the duration and the rhythm of stimulation. The threshold of excitability was determined before and after perfusion with one of the drugs, as duration of stimulation (0.05 to 50 σ) necessary to keep the heart contracting at a fixed rate of 90 per minute. Acetylcholine in concentrations of from 1×10^{-5} to 1×10^{-3} did not change the excitability in the majority of experiments. In some experiments it produced transient arrest of the heart, following which the heart resumed contractions at the same rate as before. Adrenaline did not change the threshold of excitability by more than 1 per cent. The author concludes that acetylcholine impairs cardiac automatism without reducing its excitability and that epinephrine has no effect upon the excitability of the frog heart.

PICK

Lown, B., Salzberg, H., Enselberg, C. D., and Weston, R. E.: Interrelation between Potassium Metabolism and Digitalis Toxicity in Heart Failure. Proc. Soc. Exper. Biol. & Med. **76**: 797 (April), 1951.

In a series of 10 patients in congestive heart failure, potassium depletion either occurring spontaneously with malnutrition and gastrointestinal disorders or induced by mercurial diuresis after pretreatment with ammonium chloride, was found to be associated with increased sensitivity to digitalis. In two patients there was also observed a decreased tolerance to digitalis after daily doses of 20 mg. of desoxycorticosterone acetate were used for 4 to 10 days. In one digitalized patient, digitalis toxicity was precipitated by the intravenous injection of insulin and glucose, which was followed by the development of a hypopotassemia.

From the present data, it would appear that the increased myocardial sensitivity to digitalis observed after potassium losses probably results from alterations in intracellular potassium distribution,

since no significant changes in serum (or extracellular) potassium was observed in 8 of 10 patients.

MINTZ

Levin, M. H., Adams, W. S., Beck, W. S., Goldman, R., and Bassett, S. H.: Prolonged Treatment of a Case of Periarteritis Nodosa with ACTH: The Effective Dose as Measured by Metabolic Balances. J. Clin. Endocrinol. **11:** 375 (April), 1951.

A 58 year old male with periarteritis nodosa proved by muscle biopsy was given two courses of ACTH during which careful metabolic balance studies were made. Although cure did not take place, clinical and pathologic remission occurred which was sustained for at least 14 months following cessation of therapy. There was a prompt decrease in both peripheral and bone marrow eosinophilia following institution of ACTH therapy, the decrease being parallel to the dose.

The metabolic responses to the hormone were similar to those observed in normal individuals, namely; negative nitrogen balance, sodium and chloride retention, negative potassium balance, increase in urinary and fecal excretion of calcium and phosphorus, increase in excretion of urinary creatine and uric acid, and no significant change in urinary creatinine. There was increased urinary excretion of "11-oxysteroids" and 17-ketosteroids. Hyperglycemia and glycosuria were noted each time ACTH was given. In most of the effects studied, it was shown that when the stepwise dosage schedule of ACTH was used, the maximum effect reached with the 40 mg. dose would be maintained when the dose was gradually reduced, indicating that once the adrenal cortex has received sufficient stimulation, its activity can be maintained for some time with smaller doses. This was not true however in the case of sodium and chloride retention, reduction in dosage resulting in a moderate salt diuresis.

CORTELL

Graham, A. J. P.: Effect of Tetraethylammonium Bromide on the Return of Blood-pressure in the Femoral Artery Distal to an Acute Occlusion. Brit. J. Surg. **38:** 519 (April), 1951.

Using dogs, the author studied the effect of tetraethylammonium bromide on blood pressure in the distal portion of the femoral artery after high ligation and division of this vessel. It was found that following such a procedure, a marked fall in blood pressure occurred in the lower segment of artery, but that a return began in a few minutes, and reached a constant level in about one and one-half hours. With the use of tetraethylammonium no further improvement in the rate of return of blood pressure was noted.

It was felt that the rapidity with which pulsation returned in the distal segment probably depended partly on the systemic pressure and partly on the caliber of the collateral vessels at the time of occlusion. Local anoxia was considered the possible cause of the dilatation of the latter vessels.

ABRAMSON

Acierno, L. J., and Gubner, R.: Utility and Limitations of Intravenous Quinidine in Arrhythmias. Am. Heart. J. **41:** 733 (May), 1951.

This report comprises a study of 44 patients with arrhythmias treated with intravenous quinidine. There were 32 consecutive unselected patients with various types of acute paroxysmal arrhythmias and 12 selected patients with chronic auricular flutter or fibrillation, or extrasystoles. Initially quinidine lactate was given in fractionated doses of 0.06 Gm. every three minutes. Later the schedule was modified so that a majority of patients received 0.13 Gm. every five minutes. If the arrhythmia was not brought under control after a total of 0.65 Gm., further administration was discontinued. Electrocardiograms were recorded during the entire trial period. Conversion to normal rhythm occurred in 22 of 28 patients in whom the arrhythmia was of brief duration and in none of the 16 patients with chronic arrhythmias. The effectiveness of quinidine did not appear to have any clear-cut relationship to the type of arrhythmia. The most significant factors determining the effectiveness of quinidine in restoring regular sinus rhythm were the acuteness of the arrhythmia and the absence of advanced organic heart disease. Serious arrhythmias (complete heart block, standstill, ventricular fibrillation, ventricular tachycardia) resulted from quinidine administration in five cases, leading to death in four subjects. All these subjects had advanced heart disease. The authors stress the necessity of careful supervision in the use of oral and intravenous quinidine. Quinidine is of little avail in long-standing arrhythmias and is hazardous in subjects with advanced organic heart disease, particularly in the presence of congestive heart failure or digitalis intoxication.

HELLERSTEIN

Szekeley, P., and Wynne, N. A.: The Effects of Magnesium on Cardiac Arrhythmias Caused by Digitalis. Clin. Sc. **10:** 241 (May), 1951

Six patients with serious digitalis toxic rhythms were treated with magnesium sulfate intravenously in doses of 15 to 20 cc. of 20 per cent solution. Two cases of bidirectional ventricular tachycardia were successfully interrupted, with lasting results. Of four cases of extrasystolic bigeminy, the extrasystoles were abolished in three, with lasting results, and temporarily stopped in one.

The depressant action of magnesium on heart muscle was demonstrated in experiments on cats. Its appearance in atropinized and vagotomized cats showed that this was not a vagal effect. Ventricular tachycardia and extrasystoles produced in cats by

toxic doses of digitalis and strophanthin were usually favorably affected by magnesium, but slow idioventricular rhythms were made slower.

ENSELBERG

Elkin, D. C., and Campbell, R. E.: Cardiac Tamponade: Treatment by Aspiration. Ann. Surg. **133:** 623 (May), 1951.

On the basis of a study of 18 cases of cardiac tamponade, the authors arrived at certain conclusions regarding the management of this condition. The physical findings are generally typical, and little difficulty is encountered in making the diagnosis in most instances. The patient is frequently unconscious or irrational and all signs of shock are present. The heart sounds, if audible, are weak and at times irregular. X-rays may show no deviation from the normal in the acute case even when severe tamponade is present. Fluoroscopic examination may be of more value, since it will generally reveal marked diminution or absence of cardiac pulsations.

In the authors' series, 17 of the patients were given conservative therapy, consisting either of supportive measures alone or of one or two pericardial aspirations. The latter were performed by inserting a short beveled 17 or 18 gage needle in the left fourth intercostal space or through the epigastrium just lateral to the xiphoid process. All these patients were given whole blood or other fluids intravenously. Of this number, one died a short while after pericardial aspiration was performed. The remaining case in the series was treated by operation but died while the pericardium was being closed.

It was the opinion of the authors that in the presence of tamponade a trial of conservative management with aspiration of the pericardium should be followed while the operating room is being prepared. If this gives good results, then it should be continued under careful observation. Where the procedure results in no improvement, then more radical therapy should be attempted.

ABRAMSON

Cahill, G. F., and Monteeth, J. C.: The Use of Dibenamine and Norepinephrine in the Operative Treatment of Pheochromocytoma. New England J. Med. **244:** 657 (May 3), 1951.

Two cases of pheochromocytoma which were successively treated surgically are reported. In the first patient the clinical picture simulated malignant hypertension whereas in the second the hypertension was paroxysmal in character. Dibenamine was given to both patients 24 to 36 hours prior to operation in order that the drug might still be effective during the surgical procedure and help prevent the marked rise in pressure which sometimes occurs during handling of these tumors. A dose of 5 to 7 mg. per kilogram of body weight in 300 to 500 cc. of saline, given over a period of at least one hour is recommended for this drug. Norepinephrine was used during the operation and in the immediate postoperative period to prevent hypotension. These authors share the belief that this drug is preferable to epinephrine since it increases peripheral resistance without increasing the cardiac output or producing significant arrhythmias. The recommended dose is 4 mg. in 100 cc. of saline, the rate of flow being controlled by frequent observations of the blood pressure.

ROSENBAUM

Schiller, A. A.: Mechanism of Action of Vitamin P Flavinoid (Rutin) on the Cutaneous Circulation. Am. J. Physiol. **165:** 293 (May), 1951.

The object of these experiments was to determine whether rutin influenced the transport of the crystalloid dye fluorescein across cutaneous capillaries of physiologically intact rabbits, and, if so, to attempt to explain the nature of its influence. Rutin produces strong independent vasoconstriction and also prolongs the activity of epinephrine. An adrenergic blocking agent had no effect on rutin vasoconstriction. Hence, epinephrine and rutin do not compete for the same receptor in vivo. Arterenol action was only moderately prolonged by rutin. The author suggests that rutin action does not depend on a nonspecific antioxidant property because ascorbic acid has an effect opposite to rutin. Ascorbic acid is known to protect against oxidative destruction of epinephrine in vitro. If rutin action in vivo were due to nonspecific antioxidant properties ascorbic acid action should have produced a qualitatively similar effect.

OPPENHEIMER

Bruetsch, W. L.: Penicillin Therapy of Cardiovascular Syphilis With Large Total Dosage. Am. J. Syph., Gonor. & Ven. Dis. **35:** 252 (May), 1951.

The occurrence of untoward reactions when cardiovascular syphilis is treated with penicillin has been overemphasized. Penicillin may be safely administered in unrestricted dosage from the start without any preparatory heavy metal treatment. It is questionable whether trivalent arsphenamine and bismuth have any appreciable effect on the syphilitic inflammatory changes in the wall of the aorta. Due to the extreme resistance of the syphilitic exudate in cardiovascular syphilis, a total penicillin dosage of approximately 25 million units, given in the usual daily dose of 400,000 to 600,000 units, is possibly needed to achieve the ultimate regression of the inflammatory cells from the aortic lesions. It should be realized that in far-advanced cases of syphilitic aneurysm, where the aortic wall is already paper thin, penicillin therapy will not prevent a possible rupture.

BERNSTEIN

Whorton, C. M., and Denham, S. W.: The Occurrence of the Jarisch-Herxheimer Reaction in a Patient With Gummatous Syphilitic Aortitis. Am. J. Syph., Gonor. & Ven. Dis. **35:** 255 (May), 1951.

A 27 year old Negro woman with gummatous syphilitic aortitis and aortic insufficiency died suddenly 27 hours after the beginning of penicillin therapy. At autopsy, in addition to the usual histologic changes of gummatous syphilitic aortitis, there was a marked acute inflammatory reaction in the aortic lesions. This change is interpreted as the histologic manifestation of a Jarisch-Herxheimer reaction.

The rarity of the Jarisch-Herxheimer reaction in cardiovascular syphilis is sharply contrasted with its frequency in early syphilis and in certain types of neurosyphilis. There is no convincing recorded instance of death resulting primarily from this reaction following penicillin therapy in patients with cardiovascular syphilis. In fact, the cause of death in the patient here reported cannot definitely be determined. Pulmonary embolism seems the most likely probability. The possibility of a Jarisch-Herxheimer reaction causing rapid dilatation of the aortic ring is suggested as a possible contributing cause of death. Also, the well-known occurrence of sudden death in patients with aortic insufficiency must be considered.

BERNSTEIN

Hall, M. N.: A Study on the Effects of Priscoline on Patients with Psychosis Due to Cerebral Arteriosclerosis. Connecticut M. J. **15:** 385 (May), 1951.

The arteries of the brain receive sympathetic innervation from the superior sympathetic ganglions (stellate ganglions) via the internal carotid nerves and internal carotid plexi. A sympatholytic drug might relieve spasm, if present, thereby influencing favorably the course of the disease. It was with this possibility in mind that an investigation was undertaken. Thirty female patients were given two consecutive monthly courses of Priscoline. They were divided into experimental and control groups and the following items were studied and followed: weight, blood pressure, blood urea nitrogen, blood sugar, urine albumin and microscopic, and electrocardiogram. Each patient was also given a Wechsler memory scale test.

There were no marked changes in the symptoms of these patients after one month on a dose of Priscoline 25 mg. four times a day or after another month on a dose of 50 mg. four times a day. An unexpected observation made was the salutary action of Priscoline in reducing the moderately elevated nonprotein nitrogen values in these patients. These results are not conclusive, but are suggestive and interesting. The side effects of the drug were minor, and there was no evidence of any toxicity.

BERNSTEIN

Salter, W. T., and Runels, E. A.: A Nomogram for Cardiac Contractility Involving Calcium, Potassium, and Digitalis-like Drugs. Am. J. Physiol. **165:** 520 (June), 1951.

A nomogram for cardiac contractility is presented which correlates combined effects of potassium and calcium ions and digitoxin congeners at 26 C. The calcium-potassium ratio is without significance, since the magnitude of maximal contraction in a concentration of K^+ ions of 0.0048 molar is determined by concentrations of Ca^{++} and cardiac glycoside which act synergistically. Concentrations of K^+ above or below 0.0048 molar reduce contractility.

OPPENHEIMER

Calesnick, B., Smith, N. H., and Beutner, R.: Combined Action of Cardiotoxic Drugs. A Study on the Acute Toxicity of Combined Quinidine, Meperidine, Pentobarbital, Procaine and Procaine Amide. J. Pharmacol. & Exper. Therap. **102:** 138 (June), 1951.

An investigation of the combined cardiotoxic action of several drugs was performed because the authors encountered a few accidental deaths from ventricular fibrillation after the start of a procaine infusion prior to surgery in patients who had been premedicated with quinidine, meperidine, and pentobarbital. The half-lethal dose of various combinations and doses of these drugs was determined in mice. The cardiotoxic actions of meperidine, quinidine, and procaine were synergistic in an algebraic summation. Combinations of quinidine and pentobarbital showed an antagonistic cardiotoxic effect. The addition of meperidine to this combination indicated a marked potentiation of toxicity. Studies of the combination of four drugs with quinidine, pentobarbital, and meperidine at constant doses and procaine or procaine amide administered as the variable showed a synergism with procaine and a decrease in toxicity with procaine amide.

SAGALL

Farah, A., and Mook, W.: The Action of Mercurial Diuretics on the Effective Refractory Period, Electrical Excitability and Conduction Velocity in the Mammalian Heart. J. Pharmacol. & Exper. Therap. **102:** 125 (June), 1951.

The action of the mercurial diuretics, Esidron acid and mersalyl, on dog and rabbit hearts was investigated. In toxic doses these drugs produced a decrease in conduction velocity, a decrease in electrical excitability and an increase in the effective refractory period of both auricular and ventricular

tissue. The rate of experimentally produced auricular flutter was reduced by the mercurial diuretics. This effect was reversed by the injection of cysteine, thioglycolic acid or BAL. In two of seven experiments the auricular flutter was changed to auricular fibrillation which could not be reverted by mono- or dithiols, blocking agents or by vagal or sympathetic denervation.

SAGALL

Rottenstein, H., Horwitz, O., Montgomery, H., Sayen, A., and Siems, L. L.: The Vasodilator Effects of Priscoline in Patients with Ischemic Extremities. Am. J. M. Sc. **221:** 661 (June), 1951.

Priscoline administered intravenously in doses of 30 to 50 mg. was demonstrated to increase the digital cutaneous blood flow more effectively in patients with arterial disease of the lower extremities than in normal controls. This increase in flow occurred chiefly in the toes; little difference was observed in the fingers of the two groups. A slight rise in cardiac output associated with an increase in pulse rate was observed in the patient group. An increase in systolic blood pressure was also noted. Basal vascular tone did not appear to influence the response to the drug in either group. Reflex heat applied to the trunk increased the digital cutaneous blood flow to a greater extent than did intravenous priscoline. The effect of priscoline appears to be exerted primarily upon cutaneous vessels, according to the authors.

SHUMAN

Walker, H. A., Wilson, S., Farrar, C., Langston, R. J., and Richardson, A. P.: The Cardiovascular and Respiratory Effects of 3-Hydroxy-2-phenyl Cinchonic Acid. J. Pharmacol. & Exper. Therap. **102:** 71 (June), 1951.

The effects of 3-hydroxy-2-phenyl cinchonic acid (HPC) were studied in dogs and rabbits. A typical Bezold effect—respiratory depression or apnea associated with hypotension and bradycardia—was produced by the rapid injection of 5 mg. per kilogram or more of HPC. The animals then became immediately refractory to subsequent doses. This refractoriness persisted up to eight hours. This phenomenon of tachyphylaxis was explained as the result of a prolonged blockade of the sensory receptors due to both the respiratory and cardiovascular effects of the drug. The cardiovascular and respiratory effects of HPC were shown to be reflex in nature with the sensory impulses carried by the vagus. Vagotomy abolished all the reflex effects of HPC and also of germitrine, phenindamine, and NU 1525. Atropine abolished only the cardiovascular effects of these agents.

SAGALL

Meyers, J. H., and Man, E. B.: Artifactual Values of Serum Precipitable Iodine after Clinical Intramuscular Injections of Mercuhydrin. J. Lab. & Clin. Med. **37:** 867 (June), 1951.

This investigation is concerned with the occurrence and duration of falsely low values of serum precipitable iodine (SPI) in patients who received intramuscular Mercuhydrin. All patients received 1 or 2 cc. of Mercuhydrin containing 0.039 Gm. of mercury per cubic centimeter. The serum precipitable iodine was determined whenever possible before, one or two hours after the injection of Mercuhydrin, and one to six days later.

Nine of the 12 patients had heart failure, complicated in two by hyperthyroidism. Only one of these two patients was receiving iodine and propylthiouracil. The three remaining patients had portal cirrhosis of the liver. All 12 subjects had edema. None of the patients received within a significant period any of the iodine compounds used as contrast media in roentgenography which give false high values of serum precipitable iodine.

One or two hours after intramuscular injections of Mercuhydrin the serum precipitable iodine is reduced and it may fall from 1.7 to 3.3 gamma per 100 cc. Such low figures for serum precipitable iodine are found in hyperthyroid patients. These low values are not due to any diminution of the quantity of iodine attached to the proteins of the serum, but are due to the formation of insoluble mercuric iodate or iodide during the technical processes of digestion in consequence of which iodine is not distilled. The duration of the interfering effect of mercuhydrin depends on the rate of excretion of the mercury. In most subjects the excretion is complete in 24 hours. In some patients the excretion of mercury is delayed. Such patients may have no diuresis. Since there is great variability in the rate of excretion of mercury, reliance cannot be placed on measurements of serum precipitable iodine within 48 hours or longer after an injection of Mercuhydrin.

Mercurial diuretics in general presumably show the same results as Mercuhydrin.

MINTZ

Sayen, A., Horwitz, O., and Stroud, M. W., III: Digital Cutaneous Blood Flow, Cardiac Output, Blood Pressure and Pulse Rate Immediately following the Administration of Four Potential Vasodilators. Am. J. M. Sc. **221:** 667 (June), 1951.

The action of four drugs considered to be potential vasodilators was studied by measuring their effect upon digital cutaneous blood flow, cardiac output, blood pressure and pulse rate. The agents studied included (1) Dioxyline phosphate, a papaverine-like derivative, (2) *N*-phenoxyisopropyl-*N*-benzyl-β-chlorethylamine hydrochloride, a dibena-

mine-like substance, (3) sodium salicylate, and (4) ACTH.

Patients were observed for a period of 1 to 2 hours following the administration of these drugs. None of the agents used had any immediate effect upon the circulation.

SHUMAN

Horwitz, O., Sayen, A., Naide, M., and Hollander, J. L.: Measurement of Certain Cardiovascular Responses to ACTH and Cortisone in Man. Am. J. M. Sc. **221:** 669 (June), 1951.

The authors observed the effect of ACTH and Cortisone upon digital cutaneous and mouth temperatures, cardiac output, blood pressure, and pulse rate in a group of patients with rheumatoid arthritis. Measurements of the responses of the circulatory dynamics were made before and during the period of therapy. The significant changes which occurred after several days included: (1) an increase in skin temperature of fingers of patients receiving ACTH but not those receiving cortisone; vasodilation was not observed in the toes; (2) a decrease in cardiac output dependent upon a decrease in pulse rate; (3) a decrease in mouth temperature in those receiving ACTH.

No significant changes in blood pressure were recorded. Some of the observed effects were thought to be associated with subjective improvement in the underlying disease process.

SHUMAN

PHYSICAL SIGNS

Samaan, A., and Wilson, W. H.: The Origin of the Polypnoea Accompanying Pulmonary Embolism. Arch. internat. pharmacodyn. **86:** 292 (May), 1951.

In dogs weighing 5 to 10 Kg. it was shown that the polypnea accompanying multiple pulmonary emboli is reflex in nature. The afferent impulses of this reflex travel along the pulmonary branches of the vagi from the embolized lung. The embolic polypnea is not dependent on pressure changes in the pulmonary vascular bed or in the systemic circulation. There is close resemblance between the embolic polypnea and the polypnea of the deflation reflex. It is suggested that in both cases, the impulses are probably initiated from the same receptors in the lungs and are carried by the same vagal fibers.

BERNSTEIN

Burchell, H. B., Pruitt, R. D., and Essex, H. E.: Excitation of the Isolated Ventricular Septum of the Heart. Proc. Soc. Exper. Biol. & Med. **77:** 117 (May), 1951.

It is possible to obtain electrograms on the isolated perfused dog's ventricular septum, and these show a reproducible pattern. The patterns indicate that the excitatory process travels in a complicated manner and the pattern varies somewhat from animal to animal. In some of the experiments the excitatory pathways varied over a period of time. As a basic rule, the left side of the septum was found to be activated early and the upper right side late. The apparent absence of septal electromotive forces in the electrocardiograms recorded by the usual clinical methods, which has been explained by the neutralization of potentials spreading inward from each side, is not supported by these observations on the isolated septum.

MINTZ

Semple, R., McDonald, L., and Ekins, R. P.: Radioactive Sodium (Na^{24}) in the Measurement of Local Blood Flow. Am. Heart J. **41:** 803 (June), 1951.

The authors studied the clearance rate of radioactive sodium from muscle after intramuscular injection, in order to determine whether it could be used as an indirect measure of muscle blood flow. The work was performed on 21 normal subjects and on 13 patients with intermittent claudication due to occlusive arterial disease of the lower extremities. It was found that the results obtained after exercise in patients with intermittent claudication fell within the normal range.

On the basis of the results, it was concluded that the clearance of Na^{24} did not measure muscle blood flow and that the use of this method to assess the effects of therapy in peripheral vascular disorders was not justifiable.

ABRAMSON

Keith, N. M.: The Significance of the Ophthalmoscope and of Knowledge of the Interior of the Eye. Proc. Staff Meet., Mayo Clin. **26:** 222 (June), 1951.

The retinal lesions give the examiner a glimpse of the changes and possible dysfunctions that may occur in other organs throughout the body. This is particularly true with regard to the brain. Albuminuric retinitis is almost always the result of hypertensive vascular disease whether occurring during the course of primary renal disease or as a part of a generalized arteriolar disorder. The acute albuminuric retinitis usually associated with eclampsia in the female has been noted in an adult male. The presence of albuminuric retinitis is of serious prognostic import. It was determined in a considerable series of patients with diffuse arteriolar disease with hypertension, that 90 per cent died in two years after the appearance of the retinal changes. However, albuminuric retinitis can recede, as well as the retinopathy of malignant hypertension, without definite directed therapy. With recession, the prognosis improves. The arteriolar changes which are diffusely scattered throughout the organs of the body may be functional or organic. The latter, are often sclerotic and occlusive in type and may lead

to occlusion of the central artery of the retina or its arteriolar branches. It is worth mentioning that in hypertensive diseases there has never been observed occlusion of the central arteries of both eyes.

SIMON

Kirschbaum, H.: Heart Sounds in Anoxia. J. Aviation Med. **22:** 212 (June), 1951.

When an experimental dog was made anoxic there was at first an increased rapidity in the heart sound, but as the anoxia became more severe, the heart dilated and the sounds became definitely slower. When oxygen was added a definite arrhythmia in the motion of the ventricles developed. There was also a marked discoloration and an increase in the bluish color of the heart with the engorgement of the vessels. These findings were also present in two humans studied during periods of anoxia.

BERNSTEIN

AMERICAN HEART ASSOCIATION, INC.

1775 BROADWAY, NEW YORK 19, N. Y.

Telephone Plaza 7-2045

FELLOWSHIP AWARDS

The Board of Directors, upon recommendation of the Research Committee of the Scientific Council, has approved thirty-seven Fellowship Awards totaling $185,650 for the fiscal year 1952–53. These include the continuation of nine Established Investigators, five new Established Investigators, the renewal of eleven Research Fellows, and the establishment of twelve new Research Fellows.

The awards were made as follows:

Continued Established Investigators

Bloch, Edward M., a study of the living microscopic blood, blood flow, and vessel walls in patients and experimental animals with thromboembolic phenomena, Western Reserve University, Cleveland.

Elkinton, J. Russell, cardiovascular physiology, University of Pennsylvania, Philadelphia.

Fishman, Alfred P., cardiodynamic and renal interplay in the production of congestive heart failure, Mount Sinai Hospital, New York.

Gergely, John, energetics and contractile proteins of heart muscle, Massachusetts General Hospital, Boston.

Heller, John H., metabolic and endocrine basis of hypertension and arteriosclerosis, Yale University School of Medicine, New Haven.

Merrill, John P., further development of the artificial kidney as a therapeutic and investigative tool in cardiovascular and renal disease, Peter Bent Brigham Hospital, Boston.

Mommaerts, Wilfried F. H. M., biochemistry of muscular contraction, Duke University, Durham.

Olson, Robert E., metabolism of cardiac muscle under various conditions of nutrition and endocrine balance, Harvard School of Public Health, Boston.

Tobian, Louis, Jr., relation of steroids and sodium to hypertension; role of steroid intoxication in toxemia of pregnancy; role of emulsifying forces in plasma in pregnancy; role of emulsifying forces in plasma in atherosclerosis, Harvard Medical School, Boston.

New Established Investigators

Aikawa, Jerry K., immunophysiology, Bowman Gray School of Medicine, Wake Forest, N. C.

Edelman, Isidore S., body water and electrolytes studied with tracers, Peter Bent Brigham Hospital and Harvard Medical School, Boston.

Kuhns, William J., immunological and immunochemical studies in rheumatic fever, Hospital of Rockefeller Institute, New York.

Peterson, Lysle H., volume pressure, "distensibility" of intact veins, arterial circulation with view to calculating stroke volume, integration of peripheral cardiovascular reflexes, University of Pennsylvania, Philadelphia.

Stamler, Jeremiah, experimental atherosclerosis; experimental hypertension; renal function in edema formation, Michael Reese Hospital, Chicago.

Renewal Research Fellows

Alexander, James K., hemodynamic aspects of mitral stenosis, under Robert F. Loeb, Presbyterian Hospital, New York.

Cavert, Henry M., metabolism of heart tissue investigated with isotopic technics, under Maurice B. Visscher, University of Minnesota, Minneapolis.

Conn, Hadley L., Jr., measurment of renal and hepatic blood flow; etiology of S-T segment–T wave depression pattern, under Charles C. Wolferth and Carl Schmidt, Robinette Foundation and University of Pennsylvania.

Hackel, Donald B., cardiac metabolism in intact dogs studied by venous catheterization of the coronary sinus, under Thomas D. Kinney, City Hospital and Western Reserve University, Cleveland.

Haddy, Francis J., pulmonary vascular resistance, pulmonary edema, under Maurice B. Visscher, University of Minnesota, Minneapolis.

Jorgens, Joseph, electrokymographic study of pulmonary vascular disease, under Leo G. Rigler, University of Minnesota, Minneapolis.

Khairallah, Philip A., biochemistry of heart muscle, proteins, under W. F. H. M. Mommaerts, Duke University, Durham.

Landon, Erwin J., studies on the metabolism of steroid compounds—possible relationships to cardiovascular disease, under David M. Greenberg, University of California, Berkeley.

Miller, Joseph H., development and application of a mechanical heart-lung for intracardiac surgery in the human, under Harry Goldblatt, Cedars of Lebanon Hospital, Los Angeles.

Nelson, Clifford V., electrical field of the heart, under E. C. Cherry and W. F. Floyd, Imperial College of Science, Middlesex Hospital Medical School, London, England.

Osborn, John J., continuation of work on experimental studies of methods for the interruption of the cardiac and pulmonary circulations by whole-body refrigeration and mechanical oxygenation, under L. Emmett Holt, Jr., New York University-Bellevue Medical Center, New York.

New Research Fellowships

Biggs, Max W., lipoprotein metabolism in health and disease, under John H. Lawrence, Donner Laboratory, University of California, Berkeley.

Garb, Solomon, physiology and pharmacology of isolated mammalian heart muscle, under McKeen Cattell, Cornell University Medical College, New York.

Hagans, James A., investigations of mechanisms involved in maintenance and control of vasomotor tone and peripheral resistance in man, under Eugene B. Ferris, Jr., Cincinnati General Hospital, Cincinnati.

Kibler, Robert F., splanchnic circulation and metabolism, under J. D. Myers, Duke University, Durham.

Kleinerman, Jerome I., studies of myocardial nutrition and circulation in animals by the radiosodium clearance method, under Thomas D. Kinney, Cleveland City Hospital, Cleveland.

McIntosh, Henry D., receptor areas in the control of blood volume and electrolytes in man, under James V. Warren, Emory University School of Medicine, Atlanta.

Mallov, Samuel, effects of ethyl alcohol and acetaldehyde on the metabolism of the myocardium and other tissues, under Jay Tepperman, State University of New York, College of Medicine at Syracuse, Syracuse.

Mateer, Frank M., cardiovascular effects of specific electrolyte depletion and repletion studied by means of dialysis technic and ballistocardiographic studies in the normal and abnormal subject, under T. S. Danowski, University of Pittsburgh.

Maxwell, Morton H., mechanism of anuria in man and renal dysfunction in congestive

heart failure, under John McMichael, Postgraduate Medical School of London, England.

Metcalfe, James, changes during pregnancy in the circulation and respiration of normal women and those with heart and pulmonary disease, under C. Sidney Burwell, Boston Lying-In Hospital, Boston.

Mitchell, George L., Jr., serum and muscle electrolyte studies in various disease states, under A. J. Merrill, Emory University School of Medicine, Atlanta.

Rowe, George G., a clinical study of the role of the sympathetic nervous system in hypertension evaluated via the action of sympatholytic and depressor drugs, under Charles W. Crumpton, University of Wisconsin Medical School, Madison.

COMMITTEE ON CARDIOVASCULAR CLINICS

The special meeting of the entire Committee on Cardiovascular Clinics will be held on February 21, 1952, at the Palmer House in Chicago. The meeting originally had been scheduled for last January 26, but was postponed.

Delegates from the Cardiovascular Clinics Committees of affiliated heart associations will attend the meeting, which will discuss the principles and procedures of the clinic approval system, the role of the local committees, and the problems presented by various types of cardiovascular clinics.

1952 HEART FUND

The goal for the 1952 Heart Fund campaign of the Association and its affiliates, which will be conducted during the month of February, has been set at $8,000,000. Funds raised will be used for the national program of scientific research, professional and lay education, and the development of community services. In 1951, over $5,570,500 was raised nationally to support this program.

In previous campaigns, physicians rendered useful service to the heart campaign by interpreting to their communities the necessity for supporting research and by helping to inform the public regarding the progress being made in treatment and care. They have also served as speakers and committee members. Information regarding volunteer service may be obtained from local heart associations.

EDUCATION SUBCOMMITTEE

The Executive Subcommittee of the Association's newly-formed Education Committee held its first meeting on January 21 in New York City. Members of the Subcommittee, which is under the chairmanship of George N. Aagaard, M.D., Dean, Southwestern Medical School, University of Texas, Dallas, are: Gordon Williams Blackwell, Ph.D., Director, Institute for Research in Social Science, University of North Carolina; J. Scott Butterworth, M.D., Assistant Professor of Medicine, New York University School of Medicine, New York; Miss Eckka Gordonn, Director of Social Service, Grace-New Haven Community Hospital, New Haven, Connecticut; Ira V. Hiscock, Sc.D., Chairman, Department of Public Health, Yale University School of Medicine; Philip Morgan, M.D., Chairman, Cardiovascular Disease Committee, Kansas State Medical Society, Emporia, Kansas; Mrs. Jean Ogden, Associate in Adult Education, Extension Division, University of Virginia; David Ruhe, M.D., Director, Medical Audio-Visual Institute, New York; Miss Marion W. Sheahan, Director of Programs, National Committee for Improvement of Nursing Services; and Edward Weiss, M.D., Philadelphia.

Ex-officio members of both the Executive Subcommittee and the full Committee are Louis N. Katz, M.D., Chicago; Howard B. Sprague, M.D., Brookline, Mass.; and Irving S. Wright, M.D., New York.

Other members of the full Committee include Emmet B. Bay, M.D., Professor of Medicine, University of Chicago; Mrs. Marguerite Clark, President, National Association of Science Writers, New York; Ward Darley, M.D., Dean, Department of Medicine, University of Colorado, Denver; Thomas J. Dry, M.D., Mayo Clinic, Rochester, Minn.; Richard Finnegan, Editor and Publisher, Chicago Times, Chicago; George C. Griffith, M.D., Thatcher Medical Center, Pasadena, Calif.; Walter Hager, Ph.D., President, Wilson Teachers College, Washington, D.C.; Tinsley R. Harrison, M.D., Professor of Medicine, Medical College of Alabama, Birmingham; Kenneth F. Herrold,

Ed.D., Assistant Professor of Education, Teachers College, Columbia University, New York; Chester M. Kurtz, M.D., Madison, Wis.; H. D. Mayerson, Ph.D., Chairman, Department of Physiology, Tulane University School of Medicine, New Orleans, La.; Dorothy B. Nyswander, Ph.D., Professor of Public Health Education, School of Public Health, University of California, Berkeley; Irvine H. Page, M.D., Cleveland; and Francis F. Schwentker, M.D., Pediatrician-in-Chief, Johns Hopkins Hospital, Baltimore.

NEW EDITOR FOR "MODERN CONCEPTS"

Dr. Benedict F. Massell, House of the Good Samaritan, Boston, has been named to the editorship of *Modern Concepts of Cardiovascular Disease*, the Association's monthly scientific review, to succeed Dr. Emmet Bay, Chicago. Dr. Massell has selected Dr. Gordon S. Myers, Boston, as Assistant Editor.

COMMITTEE ON SCIENTIFIC EXHIBITS

Dr. Louis N. Katz, Chicago, President of the Association, has been named Chairman of the Committee on Scientific Exhibits, to plan a special exhibit for the Chicago Session of the American Medical Association, June 9–13, 1952. The exhibit will be a cooperative effort by the American, Chicago and Illinois Heart Associations. In addition to the exhibit, daily question-and-answer sessions will be held by the AHA in a special lecture hall. Cardiologists and other scientist members of the Association will participate.

LATIN-AMERICAN NEWS NOTES

In recognition of the increasingly close relationships with the cardiologic societies of Latin America, the Publications Committee of the AHA has recommended that items of interest from the cardiologic societies of Spanish-speaking countries be included in the news section of CIRCULATION, as space allows.

INTERAMERICAN CONGRESS

The scientific sessions of the Fourth Inter-American Cardiologic Congress to be held in Buenos Aires, under the auspices of the Argentine Society of Cardiology, will take place from Monday, September 1, to Saturday, September 6, 1952.

The Congress Dinner is scheduled for September 6 at 9 P.M. During the week of September 7, excursions will be organized. Arrangements are being made to reduce the cost of transportation and lodging for those wishing to attend. President of the Congress is Dr. Pedro Cossio of Argentina.

The Association's Board of Directors recently approved the appointment of Dr. Irving S. Wright, President-Elect of the AHA; Dr. Carl J. Wiggers, Western Reserve School of Medicine, Cleveland; and Dr. Myron Prinzmetal, Cedars of Lebanon Hospital, Los Angeles, as delegates to the Interamerican Cardiological Society. They will fill two terms expiring in September and one newly created membership on the Society's governing board.

EUROPEAN CARDIOLOGICAL CONGRESS

Dr. D. Evan Bedford, British member of the International Council of Cardiology reports that the European Cardiological Congress will take place in London, England, on September 11, 12 and 13, 1952.